CHAPTER XI

NEPHRITIS IN CHILDHOOD

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INTRODUCTION

Acute nephritis occurring in childhood can be separated clinically into two main forms. This division, based on history of onset, distinctive symptoms and certain laboratory data, is supported by much pathologic evidence, so that it is possible from correlation of the clinical and laboratory features to predict with considerable accuracy the histopathology of the kidney.[1, 2, 3, 4] The two forms are designated (1) acute glomerular or hemorrhagic nephritis and (2) acute tubular nephritis. In the latter type the term nephrosis, as proposed by Muller[5] and Volhard and Fahr[6] is used quite generally, inasmuch as the histologic changes are degenerative rather than proliferative in nature. Less frequently a type of acute nephritis is seen which presents clinically a combination of features of the two main groups. It is designated acute glomerulo-tubular or mixed nephritis.

Pathologically glomerular nephritis represents a pure type only in the initial stage for in a short time there occurs secondary damage in the tubules Reciprocally, in tubular nephritis the glomeruli occasionally suffer However, the clinical course and laboratory data usually are characteristic of one or the other of these forms enough to justify separating them into these two groups for clinical purposes

The clinical and laboratory data, which serve as criteria in the division made above are shown in Table I

TABLE I

DISTINCTIVE FEATURES OF THE MAIN FORMS OF ACUTE NEPHRITIS IN CHILDREN

Features	Acute Glomerular	Acute Tubular
History of infection	common	rare
Onset	acute	insidious
Urine	blood	albumin
Non protein nitrogen	increased	normal
Serum protein	normal	low
Edema (visible)	slight	marked
Arterial tension	increased	normal
Uremia	frequent	rare
Recurrence	rare	common
Fatal termination	uremia	secondary infection

In the form glomerulo tubular or mixed nephritis are placed cases in which the onset, clinical course or laboratory data vary in one or more respects from the characteristic features of either glomerular or tubular nephritis alone Examples of these variations are an insidious onset marked edema, albuminuria, *elevated blood pressure*, low plasma protein normal non protein nitrogen or an onset following an *acute infection* with a marked pitting edema, normal blood pressure low plasma protein and periods in which the urine shows excessive albuminuria *erythrocytes* even gross blood It is interesting that in our own cases relatively few patients had to be grouped as mixed types

Incidence

The incidence in a six year period of the acute forms of nephritis in the *Infants and Children's Hospital Boston was as follows*

Acute glomerular nephritis	136
Acute tubular nephritis	29
Acute glomerulo-tubular (mixed) nephritis	13

In contrast to acute nephritis chronic nephritis occurs infrequently in childhood There were only 12 cases in our series This low incidence of chronic nephritis is accounted for partially by the limitation of the term (chronic nephritis) to include only mixed types with interstitial changes *Chronic* tubular nephritis should not be separated in childhood from the corresponding acute form the cases are all acute in onset and duration which has served alone as *the distinguishing feature is not within wide limits an adequate basis for division* In tubular nephritis the clinical picture and pathological findings are almost the same in cases of a few weeks and of several years duration and complete recovery without permanent kidney *damage* may occur after a prolonged course

There is a rare type of nephritis namely chronic diffuse nephritis which is not secondary to the acute forms but apparently is congenital in origin This *form of nephritis is also termed renal infantilism and renal rickets There have* been three patients with this condition in our series

Acute Glomerular Nephritis

Pathology

In acute glomerular nephritis the kidneys are enlarged swollen and deeply colored with the glomeruli standing out prominently Practically all of the glomeruli are more or less involved The tubules do not escape injury but show changes which probably are secondary to the glomerular injury Microscopically the glomeruli show an increase of cells and nuclei in early cases leucocytes later *excessive growth of endothelium* The circulation through the glomeruli always is impaired as evidenced by the partial or complete absence of blood in some or all of the capillaries of the tuft

Etiology

As the rule glomerular nephritis is most likely to appear following a latent *period of several days or even two or three weeks intervening after the onset of*

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The *volume of urine* is diminished sometimes slightly sometimes to the point of anuria There is a distinctive smoky color due to the presence of erythrocytes with a red sediment settling out on standing The sediment in the early stages contains all forms of casts and many erythrocytes and leucocytes The excretion of phenolsulphonephthalein is normal or slightly diminished *Cultures of the urine are sterile* *Diminution in the amount of blood is* an evidence of improvement although red and white blood cells and casts may persist microscopically for a long time On the other hand recurrences of *gross blood* frequently appear with intercurrent infections or following tonsillectomy

The concentrating power of the kidney is well preserved In most cases salt excretion remains *normal* but there is *in general* a diminished ability to excrete the end products of nitrogen metabolism As a result there is an accumulation of these substances in the blood seldom however to the point found in chronic interstitial nephritis The severity of the general symptoms apparently is not dependent on this nitrogen retention or on the volume of urine excreted *In one patient with anuria who died the urea nitrogen was 28 mgm* whereas *in another fatal case* without anuria the urea nitrogen was 115 mgm per 100 c c of blood

There is no characteristic *temperature* reaction Rather the temperature is noted for its irregularity and instability There are frequent recurrences of *fever but seldom to a high degree* *Unusual activity even a few minutes exer*tion may be followed by faintness and a rise of two or three degrees of temperature

Edema is present but in the majority of cases not to a marked degree Rarely is it visible as more than slight puffiness about the face in many cases it passes *unnoticed* *Pitting edema seldom is present* and *deposition of water* in the subcutaneous tissues or body cavities is rare As determined by frequent weighing the water retention averages around 4 to 5 pounds With improvement there is always observed a steady loss in weight and an increase in the amount of urine voided Certain cellular organs are greatly increased in weight In all *cases observed by us at necropsy the brain has weighed 20 to 30 per cent* more than the normal for the age The convolutions are flattened and the surface is firm and tense

The arterial blood pressure is elevated to a greater or less degree in all cases[7 9 10 2] While the amount of blood in the urine the degree of oliguria and the *retention of nitrogen products in the blood are accepted generally* as indices of the *severity of the condition* and *are indeed of value* the most important *danger signal* is a steadily rising blood pressure with or without the development of cerebral symptoms (headache vomiting visual disturbances *coma convulsions etc*)

Children whose systolic blood pressure remains below 110 mm may be re

an acute infection notably sinus infection, pharyngitis, otitis, cervical adenitis and especially tonsillitis The probable etiologic relationship of the hemolytic streptococcus to this form of nephritis is indicated by the frequency with which this organism is found as the inciting agent in the disease preceding the nephritis Additional evidence is offered by the production of experimental nephritis with hemolytic streptococcus toxins[7] Since the recognition of the hemolytic streptococcus as the specific etiologic agent in scarlet fever, we have included the acute nephritis of this disease in this group

Acute nephritis is exceedingly rare under two years of *age*, despite the frequency in this period, with the exception of scarlet fever of those infections which precede the disease In infancy the presence of albumin, blood and formed elements in the urine is due more often to febrile albuminuria, dehydration local kidney infection (purulent nephritis) or calculi than to nephritis In our series but two cases of glomerular nephritis occurred in children under two years of age

There is no special predisposition so far as *sex* is concerned, but, as might be expected, *season* is of some importance The incidence of acute glomerular nephritis is higher during those seasons of the year when infections of the throat and ears are most frequent The incidence varies from year to year likewise in accordance with the rise and fall of morbidity of upper respiratory infections

Symptoms and Clinical Types

In the usual form of acute glomerular nephritis the patient is taken ill with fever and malaise associated with localized infection in the throat, ears or cervical glands After being ill two or three days he improves partially or so completely as to be up and about, to play and perhaps to return to school Following an interval of a few days to three weeks, puffiness is noted about the eyes especially in the morning or perhaps the first abnormality noted is the presence of dark smoky or bloody urine Although the appetite suffers, and there is some pallor the majority of children do not appear very sick The duration of hematuria is variable The average duration in our series of cases was between four and six weeks

In severe cases following the initial infection, more alarming symptoms ensue These are headache visual disturbances vomiting of a cerebral type increasing stupor with frequently a slowing of the heart and respiratory rates generalized convulsions and coma Occasionally this train of symptoms occurs in a patient in whom hematuria, though present had not been noted previously

In contrast to these types there appear cases lasting a very short time beginning with albuminuria and large numbers of red blood cells in the sediment, which disappear completely in a few days

fracture and similar conditions The brain weighed 1,500 grams as compared with 1 00 grams the normal weight of the brain at this age The kidneys showed the anatomical lesions characteristic of acute glomerular nephritis

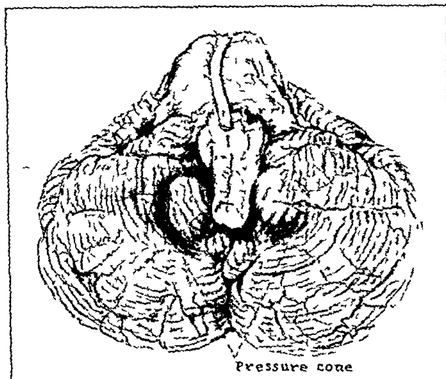


FIG. 1 Appearance of the brain of a patient succumbing to uremia of acute glomerular nephritis Note medullary cone phase compression of medullary structures flattened convolutions and indistinct sulci

Of the therapeutic measures which we have employed in the treatment of patients with acute glomerular nephritis exhibiting cerebral manifestations (uremia) magnesium sulphate has proven to be of most value Magnesium sulphate should be given by mouth and by rectum or intravenously, according to the severity of the symptoms and the degree or rapidity of rise of the blood pressure The oral and rectal administration of the salt usually suffices to control and relieve the symptoms in the majority of cases if the administration is begun with the appearance of an elevated blood pressure during the stage of headache and vomiting and before the development of coma and convulsions Very large doses of the salt are required by mouth 30 to 60 c c (one to two ounces) of a

garded as in no danger But a rise of the blood pressure above this level, particularly if it steadily increases should be taken as an indication for intensive treatment

Uremia occurring with acute glomerular nephritis constitutes a well defined syndrome with a demonstrable cause[10, 2] It is ushered in with headache, vomiting visual disturbances delirium, coma and then convulsions The optic discs may show papilledema Paralleling the course of the symptoms is a steadily rising arterial blood pressure As the systolic blood pressure rises above 140 mm, the patients may vomit and complain of headache If the rise continues, coma and convulsions often ensue Thus an increasing systolic blood pressure assumes considerable importance as a warning signal of the imminence of uremia Although convulsions rarely occur with a blood pressure under 150 mm, the degree of elevation is of relatively less importance than the rapidity of its rise In chronic nephritis the blood pressure may remain elevated to a high degree for a long period of time but this elevation is constant In acute nephritis the elevation increases rapidly and with it the severity of the uremic symptoms There may or may not be an increase in visible edema in patients with impending uremia but that a retention of fluid is taking place is shown by the gradual increase in body weight Fatal termination is preceded by pulmonary edema or central respiratory failure

The cerebral symptoms in acute glomerular nephritis are not dependent on the amount of non protein nitrogen in the blood or on the degree of hematuria They are not peculiar to uremia but are the characteristic symptoms produced by a rapidly increasing intracranial pressure[10] The association of cerebral edema and increased intracranial pressure in this form of uremia has been amply proven at necropsy

Case 1 E McG six and a half years old suffering with acute glomerular nephritis was admitted to the hospital 10 days after an acute rhinopharyngitis Because of the vomiting headache disturbances in vision and a blood pressure of 150 mm (systolic) he was given 150 c c of a 1 per cent solution of magnesium sulphate intravenously This was followed by improvement and a fall in blood pressure to 130 mm (systolic) However several hours later the blood pressure rose the child became comatose signs of pulmonary edema appeared and shortly afterwards respiration ceased

Necropsy findings —On removal of the calvarium the dura mater was found so tense that when it was opened the brain bulged through the small incision The surface of the brain was pale and moist The convolutions were flattened and there was a circular impression involving the base corresponding to the foramen magnum (Fig 1) in other words there was the medullary cone phase produced when the medulla is forced into the foramen magnum as the result of rapid increase of brain volume, as in brain tumor, hemorrhage skull

urine was dark in color there was a large amount of albumin and there were many red and white cells The non protein nitrogen was 64 mgm The blood pressure was 160 mm systolic and 106 diastolic

Course in Hospital — He was given 30 c c (1 oz) of a 50 per cent solution of magnesium sulphate by mouth and by rectum every 4 hrs The next day the blood pressure was 180 systolic and he was most uncomfortable from vomiting and headache There was a slight degree of edema of the optic nerve The treatment was continued and the following day the blood pressure was 160 mm systolic and he was having free catharsis and diuresis Thereafter the blood pressure gradually fell and the evidences of intracranial pressure (vomiting and headache) subsided When the blood pressure was at its height 180 mm the patient weighed 77 lbs Four days later he weighed 71 lbs and the blood pressure was 120 mm systolic The course of the nephritis as evidenced by the urinary findings was not altered (see Chart 1)

In comatose patients or those with convulsive twitchings the salt should be injected intravenously in dosage sufficient to lower the blood pressure The solution used for injection is made up to contain 1 per cent anhydrous magnesium sulphate (or 2 per cent of the crystals $MgSO_4 7H_2O$) This is injected slowly 3 to 4 c c per minute by gravity into an arm vein while the blood pressure is followed on the other arm As the injection proceeds the patient may perspire freely vasomotor flushes run over the body the twitching ceases and the blood pressure gradually falls The amount required has been in our cases about 10 c c per kg of body weight Should signs of respiratory depression develop from the too rapid administration of the salt the injection should be stopped for a few minutes If the depression becomes alarming it can be relieved promptly by parenteral injection of calcium chloride (2 to 5 per cent solution) This never has been necessary in our experience

Following the injection of magnesium sulphate it is necessary to continue with large doses of the drug by mouth If the water retention and cerebral edema are not reduced by the oral administration of the salt the blood pressure rises again and repetition of the intravenous injection may be required Intravenous treatment is not effective during the terminal medullary cone phase

A procedure such as lumbar puncture should be used cautiously because removal of spinal fluid may result in incarceration of the edematous brain in the foramen magnum and compression of the medulla

The following case illustrates the beneficial effect of magnesium sulphate in the treatment of the cerebral symptoms (uremia) in acute nephritis

Case 3 — The patient R K aged 6 years was admitted to the hospital with acute glomerular nephritis 10 days after an attack of tonsillitis The physical examination was negative except for a moderate degree of generalized edema The urine was smoky in color and contained albumin many red and

50 per cent solution are given every four hours until free catharsis ensues The action is apparently one of general dehydration, with resultant diminution of cerebral edema[11] Evidences of improvement are diminution in headache and visual disturbances and a fall in blood pressure Improvement is gradual and is seldom accomplished without loss of body weight

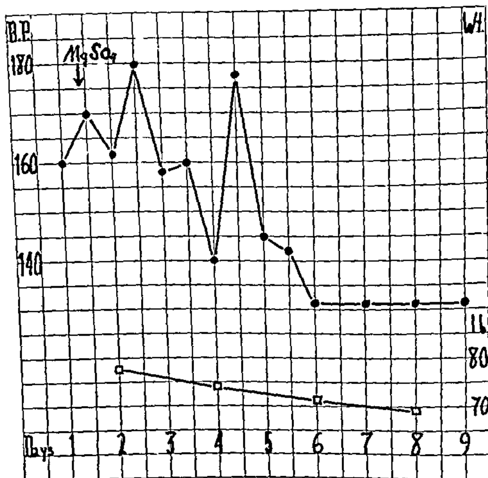


CHART 1 J G It illustrates the fall in systolic blood pressure and the loss of weight following the administration of magnesium sulphate by mouth and by rectum Upper line, systolic blood pressure lower line body weight

Case 2 —J G, aged 13 yrs 4 wks following a mild attack of scarlet fever, was noticed to be slightly swollen about the eyes An examination of the urine revealed a large amount of blood The following day he complained of headache and epigastric pain and vomited On admission to the hospital the physical examination was negative except for slight edema of the face The

became irrational and had a convulsion One hundred and fifty c c. of a 1 per cent solution of magnesium sulphate were then injected intravenously During the injection (18 min) the systolic blood pressure fell to 115 mm and the cerebral symptoms subsided A second injection was given after 5 hours as the blood pressure had risen to 145 mm systolic and headache was more pronounced Catharsis was induced by 60 c c (2 oz) of a saturated solution of magnesium sulphate every 4 hours by mouth Three days later with the blood pressure remaining at a low point (110 mm) the patient complained of no cerebral symptoms He weighed 36½ pounds a loss in weight of 3 pounds His subsequent course was uneventful (see Chart 2)

Prognosis

Patients with glomerular nephritis usually recover There are no criteria associated either with gravity of renal symptoms or within wide limits with duration which aid in determining the cases which will make a complete recovery When death occurs in the acute stages it is due usually to uremia Various observers[12, 13] in examining adults, who had had glomerular nephritis in childhood found that less than 10 per cent showed persistence of renal symptoms

Prophylaxis

We are helpless to prevent an attack of nephritis following infection Hygienic and therapeutic measures such as rest in bed forcing of fluids restriction of diet, and even specific therapy as serum in scarlet fever do not seem to alter the incidence or the course of the disease

Treatment

Ordinarily the child with acute glomerular nephritis should be kept in bed so long as hematuria persists If renal signs are unusually protracted and systemic symptoms have subsided limited activity may be permitted

Restriction of the diet has been widely advocated in the treatment of this type of nephritis Recently however there has developed a more liberal attitude toward the dietetic treatment[14] So-called standard nephritic diets often are restricted to such an extent as to be needlessly distressing or even harmful to the patient To keep rapidly growing children on low protein, low salt diets with restricted water intake has little influence on the disease and may result in failure of the general condition of the child Nutritional edema has occurred in nephritic children kept on low protein diets over prolonged periods of time

white cells and granular casts The non protein nitrogen was 30 mgm per 100 c c of blood The urinary output in the first 24 hours was 780 c c and the fluid intake was 1200 c c The phenolsulphonephthalein test showed 45 per cent excretion in 2 hours

Course and Treatment — On admission the patient weighed 38 pounds The systolic blood pressure was 120 mm During the next few days there was a

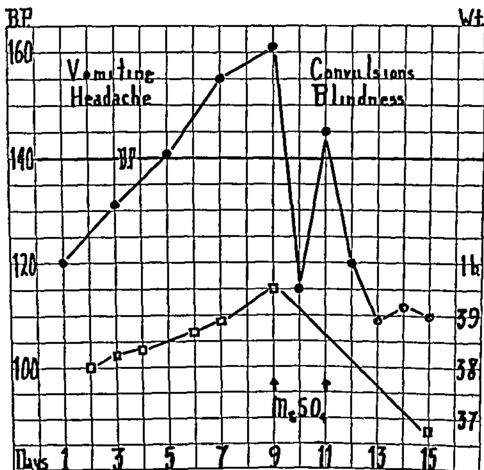


CHART 2 R K It indicates the association of the symptoms of uremia with increasing blood pressure and increasing weight and a prompt fall in blood pressure following intravenous injection of $MgSO_4$ solution (1 per cent) with loss in weight Upper line systolic blood pressure lower line body weight

steady increase in weight and a gradual increase in blood pressure The patient vomited frequently and seemed most uncomfortable from headache When the blood pressure reached 160 mm systolic the patient weighed 39½ pounds, a gain of 1½ pounds in 6 days He complained of difficulty in seeing suddenly

consists in giving 150 to 200 gms of sugar in the form of syrup lemon juice may be added to improve the flavor[6] We have not used this procedure but have relied on observation of the blood pressure to determine the danger of impending uremia and have used magnesium sulphate (as described above) to prevent the development of cerebral symptoms

The importance of following the blood pressure cannot be over-emphasized If the systolic pressure rises above 140 mm a determination should be made every 6 to 8 hours until the pressure has fallen to a lower level as a very important means of following the progress of the disease

As soon as the child has recovered from the more acute stage attention is directed toward clearing up of foci of infection If the tonsils and adenoids are obviously infected and if their removal can be expected to improve the general condition of the child operation frequently is performed early in the course of the disease

Acute Tubular Nephritis

Etiology and Pathology

The etiology of the type of acute tubular nephritis which occurs in childhood is not known Infection either focal or systemic has been suggested as the underlying cause for the development of this disease but confirmatory evidence is lacking[15 16 17 21 22]

The kidneys are large and pale The capsules are not adherent In section the cortices are thick and flecked with yellow Microscopically the abnormalities are most marked in the tubules The epithelium especially in the convoluted tubules is swollen and granular or atrophic Numerous hyaline casts are present in the tubules The glomeruli are damaged only slightly and the interstitial tissue appears normal The amount of fat and lipoid in the cells and casts varies greatly[1]

In the liver occur changes consisting of atrophy and degeneration of the hepatic cells The thyroid gland may show absence of colloid atrophy and desquamation of epithelial cells and extreme vascular engorgement[21]

A number of investigators have expressed the belief that the etiologic agent does not act primarily upon the kidneys and that the important clinical manifestations in this disease are dependent upon a systemic disturbance which produces secondarily the anatomical changes in the kidneys[18 19 20 21] Others believe that the renal lesion is of primal importance

Tubular nephritis is rare in infancy although cases have been reported in infants under one year of *age* *Sex* is not an important factor and unlike hemorrhagic nephritis the morbidity is not influenced by *season*

In a disease of such long duration an effort should be made to supply a well balanced diet adequate for maintenance of the energy and structural needs of the child In the absence of cerebral manifestations (uremia) and as soon as the patient s appetite returns we use a diet consisting of potato, cereals green vegetables, fruit juices milk eggs and small amounts of meat A sample diet is given

Illustrative Diet

Breakfast	Cooked cereal Bread Butter Milk
Mid morning	Orange juice
Dinner	Soup Meat or egg Macaroni potato or rice Peas spinach green beans carrots or beets Bread Butter Custard rice or bread pudding ice cream or sherbet
Supper	Cooked cereal Bread Butter Stewed fruit

We have compared a series of cases maintained on a low protein low salt diet with our recent series maintained on a liberal diet and have found that the use of a liberal diet has not been followed by increase in the duration of the acute stage of the disease or in the frequency of the incidence of chronic nephritis It is noteworthy that when renal symptoms have subsided and patients are ready to resume normal activity children maintained on a liberal diet are strong and vigorous and do not require weeks or months to regain normal weight and strength

Ordinarily no restriction of fluids is required in cases of acute glomerular nephritis

The patient should be weighed at frequent intervals The intake and output of fluid should be recorded and the urine examined at intervals If the patient becomes anuric hot rectal irrigations hot kidney packs or hot baths may be helpful measures

A major part of the treatment of acute glomerular nephritis consists in measures directed toward the prevention of uremia In many clinics sugar days are used for this purpose Sugar burns without ash, sparing the kidney discharge of water and rinsing out of dissolved substances sets in promptly Sometimes in impending uremia 8 to 10 sugar days are allowed in succession The procedure

in less concentration Even in stages of water retention kidney function for dissolved substances is well maintained as shown by the high concentration of the urine and the lack of nitrogen retention in the blood Water apparently is not available or cannot be excreted Phenolsulphonephthalein excretion is normal Doubly refractile lipoid bodies may be found in large quantities in the urine

The concentration of the *blood* is normal except for slight dilution in the period during the loss of water from the tissues Cholesterol in the blood is increased The inorganic constituents show no remarkable deviation from the normal[7, 8] The hemoglobin content of the blood is not remarkably changed and the white blood count while usually normal in uncomplicated cases may be elevated even in the absence of undetermined process of infection The serum protein constantly is reduced and there is an alteration of the albumin globulin ratio in the plasma presumably the result of the excretion of the albumin in the urine As mentioned above, non protein nitrogen is not increased

The *blood pressure* may be slightly elevated but this elevation usually subsides in a few days The average blood pressure in our series was 95 to 105 systolic an elevation of 5 to 10 points over the normal for the age group involved

Despite the large accumulations of edema fluid there is seldom hypertrophy of the heart or embarrassment to respiration

In the absence of secondary infection the *temperature* of patients with this form of nephritis remains within normal limits

Prognosis

Acute tubular nephritis as a rule shows a prolonged course frequently drawn out over many months with remissions lasting for variable periods The general condition of the patient suffers a severe injury through the repeated attacks and frequently through ill advised limitations of diet Occasionally complete healing occurs after a long duration of the disease optimism regarding prognosis is tempered by the realization of the constant menace of secondary infection

In any disease of such long duration with misleading and variable remissions mortality statistics are of diminished value unless the period of observation be very long Likewise percentages of complete recoveries are open to question and certainly evaluation of therapeutic procedures becomes most difficult

In Davison and Salinger s[4] series the mortality was 3 per cent but complete recoveries numbered only 20 per cent Clausen[9] in a similar series found a mortality of 43 per cent In our own series of 29 cases there were 11 deaths (a mortality of 38 per cent)

Symptoms and Signs[22 23 24 2]

The onset of the condition is insidious, seldom is there an acute infection immediately antedating the illness A child who has been regarded as entirely well, is noted to have a puffiness about the face or about the ankles The edema spreads until it may involve the subcutaneous tissue to an extreme degree as well as the serous cavities The patients are not very sick, except as they are rendered miserable irritable or embarrassed by the accumulation of edema fluid As the accumulation of fluid increases the eyes are closed, the legs are tremendously swollen, and the abdomen is distended and tense with fluid in males the scrotum and penis are painfully edematous There are no other outstanding constitutional symptoms characteristic of this form of nephritis (Fig)



FIG A child of 5 years in the edematous stage of acute tubular nephritis Note oedema of face abdomen and lower extremeties

A curious manifestation is the tendency of the edema to shift suddenly from one part of the body to another Also there are sudden and inexplicable changes in the degree of edema A child may lose as much as 9 to 12 pounds in 2 or 3 days and then after a variable period reaccumulate as much or more fluid in an equally short time Remissions and exacerbations of degree of edema and albuminuria constitute the most important feature of the disease Seldom does a child escape without more than one attack The duration of remissions is quite variable in some cases lasting only a few weeks in others persisting for several months, during which the child appears perfectly well

The *urine* is characteristic During the edematous stage the amount is small, the specific gravity is high and there may be as much as 10 to 20 per cent of albumin The sediment contains large numbers of casts of all types numerous leucocytes but *almost no erythrocytes* As the edema lessens the urine volume increases, the specific gravity falls, but albumin persists although

in less concentration Even in stages of water retention kidney function for dissolved substances is well maintained as shown by the high concentration of the urine and the lack of nitrogen retention in the blood Water apparently is not available or cannot be excreted Phenolsulphonephthalein excretion is normal Doubly refractile lipoid bodies may be found in large quantities in the urine

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In Davison and Salinger s [3] series the mortality was 32 per cent but complete recoveries numbered only 20 per cent Clausen [9] in a similar series found a mortality of 43 per cent In our own series of 29 cases there were 11 deaths (a mortality of 38 per cent)

Death is due almost always to secondary infection Despite their lowered resistance, many patients go safely through repeated mild infections, and have passed uneventfully through such diseases as measles, scarlet fever, and streptococcus cellulitis

Case 4 — C P a boy of $3\frac{1}{2}$ years in the edematous stages of nephrosis went first through a severe attack of cellulitis of the thigh and subsequently through an attack of measles making uneventful recoveries from both, to succumb at the end of 6 months to streptococcus peritonitis

Treatment

The child should be kept in bed throughout periods of edema Limitation of fluids causes discomfort to the child and does not reduce the edema On the other hand too free allowance of water results in unnecessarily rapid and embarrassing accumulation of the edema fluid

A Sample Diet for Child of 4 yrs Containing 70 gms of Protein

Breakfast	Orange or 10% fruit	1	100 gm
	Soft boiled egg	1	50 gm
	Milk (whole)	1 cup	240 c c
	Butter	1 sq	10 gm
	Toast	1 slice	30 gm
Mid morning	Milk	1 cup	240 c c
Noon	Cream soup (milk and strained vegetable)	½ cup	120 c c
			30 c c
	Butter	2 sq	20 gm
	Baked potato		60 gm
	Scraped beef	small piece	45 gm
	Vegetable		60 gm
	Bread	half slice	
	Junket	2 tbsp	
Evening	White meat of chicken		30 gm
	Toast	half slice	15 gm
	Butter	1 sq	10 gm
	Peas	1 tbsp	30 gm
	Milk	1 cup	240 c c
	Gelatin desert	1 serv	
	Fruit	¼ cup	60 c c
	Totals Calories 1459 Carbohydrate 117	Protein 70	Fat 79

Total fluids in diet 720 c c

The diet should be adequate for maintenance of the structural and energy needs of the child with an additional allowance of protein to compensate the loss of albumen through the kidneys In a disease of such prolonged duration diets restricted in one or more essential elements (notably salt free diets) must be used cautiously if one is to avoid injuring the general condition of the rapidly growing child

Of utmost importance is the removal of foci of infection and the prevention of acute infections in the child with tubular nephritis The drainage of an obvious infection often results in release of edema fluid Infections however slight allowed to remain may become the primary focus from which organisms are disseminated to the blood stream or to one or another of the accumulations of edema fluid

Reduction in the amount of edema fluid cannot be accomplished readily and dependably by any series of procedures Occasionally diet seems to influence the edema A diet high in protein and low in fat as suggested by Epstein[29] on the basis of the blood findings is not a dependable means of reducing edema Sometimes marked loss of weight has followed its use but a second attempt in the same patient has met with failure This also has been our experience with the low protein and salt free diets Likewise the removal of foci of infection has resulted in marked loss of weight In general medication has been disappointing Sweating induced by hydrotherapy or drugs has little effect Many diuretics have been advised each occasionally seems effective but few equal the claims advanced for them and none is dependable The nature of the disease with its tendency to sudden remissions renders difficult the evaluation of the effect of drugs One wonders if the improvements attributed to drugs were not sometimes spontaneous remissions The list of those substances which have received trial includes acid producing salts alkalies cathartic salts caffeine urea theocin diuretin salyrgan and novasurol[30, 31, 32, 33, 34, 35, 36, 11, 37, 38, 39] Thyroid sometimes is effective[40, 41] It has been suggested that the dosage used has been too small but we have been disappointed even when large amounts of thyroid extract have been given over a long period of time

Blood transfusion combatting low serum protein is temporarily effective Decapsulation of the kidneys has not been effective in our experience

If the accumulation of edema fluid becomes too great with consequent embarrassment of the heart or respiration it may be necessary to withdraw fluid by abdominal paracentesis Removal of fluid in this manner almost always results in some temporary diuresis and general improvement of the patient We have seen a child lose 15 to 20 pounds after the removal of 2 or 3 litres of ascitic fluid The improvement is temporary and one must never lose sight of the danger of infection in any operative procedure on these patients

An instructive case of nephrosis showing remissions ineffectiveness of

Death is due almost always to secondary infection Despite their lowered resistance many patients go safely through repeated mild infections, and have passed uneventfully through such diseases as measles, scarlet fever, and streptococcus cellulitis

Case 4 — C P a boy of [illegible] years in the edematous stages of nephrosis went first through a severe attack of cellulitis of the thigh and subsequently through an attack of measles making uneventful recoveries from both to succumb at the end of 6 months to streptococcus peritonitis

Treatment

The child should be kept in bed throughout periods of edema Limitation of fluids causes discomfort to the child and does not reduce the edema On the other hand too free allowance of water results in unnecessarily rapid and embarrassing accumulation of the edema fluid

A Sample Diet for Child of 4 Yrs Containing [illegible]0 Gms of Protein

Breakfast	Orange or 10 fruit	1	100 gm
	Soft boiled egg	1	50 gm
	Milk (whole)	1 cup	240 c c
	Butter	1 sq	10 gm
	Toast	1 slice	30 gm
Mid morning	Milk	1 cup	240 c c
Noon	Cream soup (milk and strained vegetable)	½ cup	120 c c
			30 c c
	Butter	2 sq	20 gm
	Baked potato		60 gm
	Scraped beef	small piece	45 gm
	Vegetable		60 gm
	Bread	half slice	
	Junket	2 tb p	
Evening	White meat of chicken		30 gm
	Toast	half slice	15 gm
	Butter	1 sq	10 gm
	Peas	1 tb p	30 gm
	Milk	1 cup	240 c c
	Gelatin desert	1 serv	
	Fruit	½ cup	60 c c
	Totals Calorie 1450	Carbohydrate 117	Protein 70 Fat 79
	Total fluids in diet [illegible]20 c c		

Ammonium chloride likewise was without benefit The protein content of the diet was increased the child continued to gain weight and theocin and caffein were given These measures had no effect on the edema In 6 days the weight increased from 36 pounds to 38¾ pounds Caffein was omitted and the patient was given diuretin The edema continued to increase 3 days later the weight reached 40 pounds and was then stationary The protein in the diet was increased to 60 gms and subsequently to 70 gms This change in diet seemed to have some effect on the edema He was discharged free from edema 3 weeks later weighing 31¼ pounds Albumin and cellular elements remained present in the urine

A few days after discharge although he was kept on the high protein diet the urinary output began to diminish and the edema to recur He was returned to the hospital (fourth admission) for this reason The temperature varied between 99 F and 102° F for 10 days It then rose rapidly and remained around 102° F to 104° F until he died 1 days later With the terminal rise in temperature the edema increased markedly and the patient complained of pain in the region of the right kidney Tenderness became marked in this region as well as over the abdomen With the question of a perinephric abscess or a generalized peritonitis in mind an exploratory incision was made over the right kidney Pus was not found The kidney capsule was stripped (Edebohl s operation) without any benefit to the patient He rapidly became worse and died a few days later Non hemolytic streptococcus was recovered from the peritoneal fluid

Laboratory Data — 1st Admission The w b c were 24 900 per cu mm 75 per cent were polymorphonuclear in type *Urine* Specific gravity 1020–1032, albumin (0 5 to 1 gm per cent) granular and cellular casts many w b c an occasional r b c non protein nitrogen 30 mg per 100 c c Phenol sulphonephthalein test 75 per cent (2½ hours) Plasma protein 5 75 per cent Fixation test normal

2nd Admission Urine Specific gravity 1020–1035 albumin (4 8 gms per cent), hyaline and granular casts and w b c W b c 16 000 to 40 000 (60 per cent polymorphonuclears) Non protein nitrogen 28 mg per 100 c c. Chlorides 533 Cholesterol 397 Serum protein 5 23 Blood pressure $\frac{100}{60}$ Phenolsulphonephthalein 40 per cent

3rd Admission Urine Specific gravity 1010 to 1020 albumin (3 gms per cent) many hyaline and granular casts and w b c Blood pressure $\frac{110}{60}$ to $\frac{65}{40}$

Summary — The diagnosis of acute tubular nephritis was made by the appearance of albumin and edema without an antecedent infection and without evidences of a focus of infection by exacerbations sometimes but not always initiated by an intercurrent infection and by remissions at which times the patient was free from symptoms The clinical findings were correlated with the

therapy, necessity of care in drawing conclusions about recovery and intercurrent infections through which a child may pass, follows

Case 5 — The patient N G was under observation from the onset of albuminuria and edema at 19 months of age until he died of generalized peritonitis when 3^{1} years old When first seen he had been ill for 2 weeks with generalized edema and albuminuria In so far as could be ascertained the edema was not preceded by an acute infection and physical examination revealed no evidence of a local or general infectious process The temperature was 101 5° F on admission but remained normal throughout his stay in the hospital (4 mos) with one exception when it rose to 103° F for 5 days No explanation was found for the fever at that time During his stay in the hospital (4 mos) there were two periods in which the edema practically disappeared, the urinary output increased and there was a lessened albuminuria. In the first period he lost 5' pounds in 6 weeks in the second period he lost 5 pounds in 8 weeks At the end of this period he was discharged much improved Albumin and cellular elements, however continued to be found in the urine Various measures to influence the edema were tried without striking results He remained at home 8 months In this interval the course was characterized by remissions and recurrences of edema The edema became excessive during an attack of mumps and the daily urinary output dropped from an average of 560 to 6 0 c c. to 1 0 to 150 c c. The urine continued to contain albumin and cellular elements On the second admission (one year after onset) he showed generalized edema and albuminuria No evidence of local or generalized infection could be found

On this admission (the second) he was observed over a period of 3 months There was one remission in which he lost 5 pounds in 2 weeks Thereafter the edema remained stationary until without apparent cause it entirely disappeared The effect of high protein diet was tried as on the former admission without noteworthy results There was a lessened amount of albumin and fewer cellular elements in the urine when he was again discharged Following this discharge his general health and appearance remained good but there was always a slight trace of albumin in the urine During the winter he had diphtheria The edema and albuminuria returned but gradually disappeared. He was admitted for the third time (nearly one year after second admission and almost exactly 2 years after the original onset) because of a recurrence of the edema and albuminuria These symptoms had recurred . weeks before and were associated definitely with an acute respiratory infection and an acute parotitis The temperature fluctuated between 98 F and 100° F The patient was observed in the hospital over a period of 4 months during which various therapeutic measures were tried Calcium chloride resulted in temporary loss of weight, but repetition of the course of treatment had no effect.

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laboratory data which showed a normal non protein nitrogen, a low serum protein, an albuminuria normal phenolsulphonephthalein excretion and a normal blood pressure

Necropsy Findings — There was an acute peritonitis which proved to be due to an hemolytic streptococcus The spleen weighed 60 grams It was dark red, firm, with indistinct markings of cut surfaces Microscopically there proved to be a depletion of lymphoid cells in the reticular tissue and numerous large mononuclear phagocytes in the pulp and blood vessels The arteries showed a degree of hyaline thickening of their walls unusual at this early age

The liver weighed 4 0 grams It showed a fine yellowish mottling The color as a whole was pale, and cut surfaces were cloudy in appearance The gall bladder and bile passages were normal Microscopically there was a moderate degree of fatty infiltration in the form of large drops at the peripheries of the lobules The liver cells throughout were reduced in size and showed marked acidophilic staining and fine vacuolization and there was much granular debris between liver columns and sinusoids There was much separation of liver cells so that the columns appeared disorganized No necroses were present

The bladder and genitalia were normal

The right kidney weighed 116 grams the left 120 grams They were enlarged pale succulent with obscured markings The cortex measured 0 5 cm to 0 7 cm in depth and was finely mottled with opaque yellowish lines and dots The glomeruli were visible with difficulty as red points

Microscopically the glomeruli were essentially normal A few showed an increase of cells in the capillaries polymorphonuclear leucocytes and mononuclear cells presumably from the endothelium, attributed to the effects of the streptococcus peritonitis

The convoluted tubules throughout the many sections taken from both kidneys showed striking change The proximal convoluted tubules were dilated, occasionally infolded and usually contained much granular detritus and circular reticulum The epithelial cells were either swollen or diminished in size, the cytoplasm granular and finely vacuolated and occasionally with colloid droplets Some swollen granular cells seemed to be discharging portions of their cytoplasm into the lumen of the tubule elsewhere the cells were much reduced in size The nuclei in general were normal and cells showing evidence of actual necroses were rare Mitotic figures were found occasionally The distal convoluted tubules showed similar but less striking changes The Henle s loops showed slight or doubtful changes The collecting tubules showed finely vacuolated cells The Henle tubules distal convoluted and collecting tubules contained many deeply staining casts of hyaline material In the cortex were a few minute cicatrices most of them of compact fibrous tissue Some however, contained many lymphoid and plasma cells and rarely one contained a resid

ium of necrotic tubule Occasionally such cicatrices were in contact with fibrosed glomeruli These cicatrices we interpreted as the result of repair following complete necrosis of tubules

Fat stains showed considerable amounts of fat in the convoluted and collecting tubules in the form of small droplets Most of the fat stained deep red with scharlach R and pink or red with nile blue sulphate

The important lesions of these kidneys were in the convoluted tubules The slight glomerular changes were those seen usually with an acute streptococcus infection In spite of the clinical evidence of long standing recurrent renal disturbance the microscopic study revealed only a rare minute cicatrix The lesions were degenerative in type

Chronic Nephritis

Patients with acute hemorrhagic nephritis who do not recover completely may develop chronic nephritis[4] a glomerulo-tubular involvement with interstitial changes As mentioned previously this occurs relatively infrequently The clinical picture varies with the nature and extent of the kidney lesions

The urine usually is of a clear pale appearance but it occasionally may contain gross blood It contains large amounts of albumin in some cases in others albumin is present only in slight traces Small numbers of red and white blood cells and casts may be found in the sediment Often the concentrating power of the kidneys is reduced The excretion of phenolsulphonephthalein may be diminished

In mild cases in addition to the urinary findings the symptoms are a waxen pallor of the skin and edema especially of the face General weakness loss of weight recurring headaches and vomiting often occur The blood pressure is elevated as the condition progresses hypertension becomes more marked occasionally reaching 170 or 190 mm mercury Often the non protein nitrogen in the blood is increased

In severe cases the patient complains of difficulty in vision and ophthalmoscopic examination shows neuroretinitis sometimes retinal hemorrhages Uremic symptoms or evidences of secondary infection are the terminal manifestations The urinary findings and the chemical changes in the blood are essentially the same as those found in chronic nephritis in the adult Recovery is rare and is seldom complete

Chronic Diffuse Interstitial Nephritis

There occurs in children a chronic interstitial nephritis of unknown etiology probably congenital which results in marked inhibition of growth[43, 44, 45, 46, 47, 48, 49, 50, 51, 52]

Signs of nutritional disturbance usually are noted in early infancy As the child becomes older, there is refusal of food and backwardness in physical

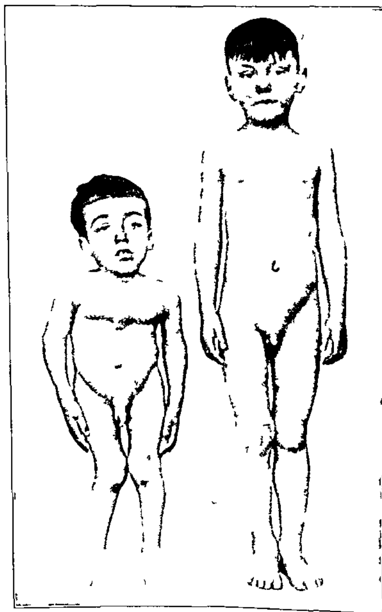


FIG 3 A child of 7 years suffering from chronic diffuse nephritis compared with a normal child of the same age Note the retardation of growth and the rachitic like deformities in the child with the congenital type of nephritis

development The bony structure is small weak and often the site of pronounced deformities which cannot be distinguished clinically or by roentgenogram from the deformities of rickets These may be noted as early as the end of the first year and are the basis for the names renal infantilism and renal rickets assigned by the English writers The character and appearance of the deformities are illustrated in Fig 3

Anemia generally is present in these patients There is often polyuria and associated increased thirst The urine volume is large the specific gravity is low Albumin is present in small amounts or it may be absent Casts are of infrequent occurrence Phenolsulphonephthalein excretion is reduced

The cardio-vascular system may show little involvement despite the prolonged duration of chronic nephritis Hypertension is likely to be absent in younger patients It is present however in children who survive to the age of 7 to 12 years In these older children atheromatous changes usually appear in the vessels, and there is cardiac hypertrophy Visual disturbances and neuroretinitis may occur The termination of the disease is in secondary infection notably bronchopneumonia or in the development of uremia

From a comparative point of view it may be said that this form of congenital kidney affection presents essentially the same picture as that of primary chronic diffuse nephritis of the adult with the difference that the nutritional disturbance is more marked in the child and the cardio-vascular phenomena more striking in the adult

Pathologically the kidneys show a fibrosis quite as extensive in younger children as in the older ones The organs are small pale and atrophic the capsule is slightly adherent Both glomeruli and tubules show extensive damage and there is considerable increase in the interstitial connective tissue

This condition seems quite definitely congenital and not due to infection in the child Greene[18] presents evidence of a familial origin of the disease

Recovery from the coma or convulsive stage of chronic nephritis or chronic diffuse interstitial nephritis is rare Palliative measures in the form of sedatives are indicated Morphine sodium luminal or magnesium sulphate subcutaneously may enable one to control the convulsions The therapy so beneficial in uremia of acute nephritis is not effective in these cases The improvement, if it occurs is transient and cannot be maintained

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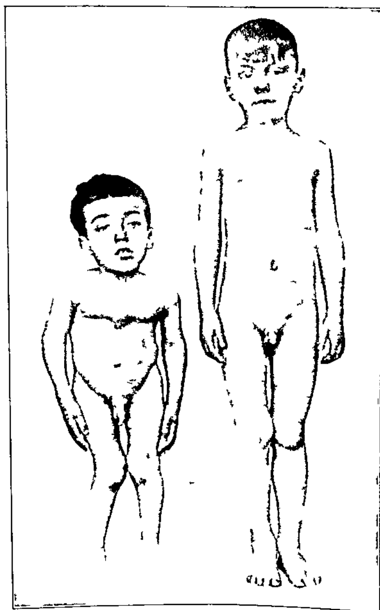


Fig 3 A child of 7 years suffering from chronic diffuse nephritis compared with a normal child of the same age Note the retardation of growth and the rachitic like deformities in the child with this congenital type of nephritis

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CHAPTER XII

WAR NEPHRITIS

By SIR JOHN ROSE BRADFORD

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The term "War Nephritis" or "Trench Nephritis" has been applied by writers rather generally to the nephritis that occurred among the troops during the European War of 1914-1919. Although the disease presented clinical features differing in some respects from that seen commonly in civil practice, yet it is very doubtful whether these differences are really sufficient to justify a special nomenclature. The term "Trench Nephritis" is certainly unsuitable inasmuch as many cases occurred in men who never served in the trenches and whose duties were performed far from the front and on the lines of communication. The term "War Nephritis" is more suitable provided it is understood to mean nephritis in war, rather than a special, peculiar, or still less a new disease.

HISTORY

Nephritis has not been a prominent disease in former campaigns with the exception of the American Civil War. During this struggle, and especially in the years 1862-1863, the case incidence of nephritis was very similar to that

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HISTORY

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seen in the British Armies in Flanders in 1915 1916 and 1917 and hence the number of cases of the malady was larger the highest rate of incidence was 1 1 per 1 000 men There the malady did not become sufficiently prevalent to be important from a military point of view except in so far as it resulted in much invalidism

In the British Armies in France and Flanders the outbreak of the disease was peculiar in that although the campaign began in August 1914 cases of nephritis were conspicuously rare until the Spring of 1915 During October November and December 1914 and January 1915 cases of nephritis were almost unknown in British military hospitals in February a few cases were admitted and then from March onwards the disease became increasingly prevalent and remained so throughout the year and also in 1916 and 1917

Etiology of War Nephritis

Climate—On the whole the disease was more prevalent in the winter than in the summer months with the exception that it was rare during the first winter of the war This is remarkable seeing that the winter of 1914 was cold and very wet on the other hand the troops at this period were mainly seasoned men but the conditions owing to military exigencies were very severe and the men were necessarily much exposed to climatic conditions as trench warfare had not developed to the extent it did later

Age—The disease has occurred among the troops in all ages from 15 to 56 years nearly 70 per cent of the cases have been in men under 35 years of age and at least 25 per cent of the total cases have been in men under 25 years of age It is clear therefore that the disease is not one affecting only or even mainly the older men

Length and Character of Service in the War Zone—The disease although not unknown was rare in men who had been overseas for less than two months The greater number of cases occurred in men who had served six months or less

Men belonging to all branches of the service were affected and the disease was by no means limited in its incidence to men actually serving in the trenches thus hospital orderlies who had never left a base hospital were attacked as well as a considerable number of men who had only served on the lines of communication The malady was decidedly uncommon among officers but the most remarkable fact was the practically complete immunity of the Indian troops* The disease was almost unknown among these Indian

* Only three cases of nephritis including chronic nephritis are known to the writer as having occurred in the Indian troops

troops in 1914 1915 although rife among the British troops in this period and although the Indian troops suffered severely from exposure to the wet and cold being especially prone to bronchitis and lobular pneumonia of a grave type

Previous Renal Disease—In 10 8 per cent of a consecutive series of 571 cases a history suggesting a previous attack of renal disease was obtained that is to say they had either suffered from a previous attack of like character *e g* with dropsy or else they stated they had had inflammation of the kidneys or Bright's disease It is possible that the proportion of cases in which a former attack of nephritis had occurred is really higher as such attacks may and do escape notice unless dropsy or hematuria are marked In the great majority of these cases there was no evidence to suggest the presence of chronic renal disease and hence it is probable that a recurrent attack of nephritis had occurred rather than an exacerbation of a chronic lesion In a few cases and more especially in some of the fatal cases there was distinct evidence of chronic disease and what had been regarded as an acute attack was really an acute exacerbation of chronic or latent disease

Pre existing Albuminuria—The examination of 50 000 healthy soldiers by Captain MacLean revealed the fact that albuminuria in some degree was present in 5 per cent and that in approximately per cent casts were also present of a character to suggest the presence of a definite renal lesion His observations also proved that the great majority of cases of nephritis occurred in men whose urine was known to be free from albumin some months before Hence it may be concluded that this nephritis is not in the great majority of cases either an exacerbation of a chronic lesion nor a sequel of a mere albuminuria Furthermore Captain MacLean has shown that neither the training undergone by recruit nor long service materially affects the incidence of albuminuria and hence it is probable that they have also little to do with the causation of nephritis

Diet—There is no evidence that diet or poisons (metallic) played any part in the etiology of the disease nor that the toxic gases employed in gas warfare had any influence in its production as nephritis was only a rare complication of gas poisoning and the outbreak of nephritis occurred several months before the introduction of gas warfare by the enemy

Illness Prior to the Onset of Nephritis—Nephritis in civil practice is well known as a sequel of a number of infections and not infrequently these infections are of a comparatively *trivial nature* such as tonsillitis catarrhs etc The original illness is sometimes overlooked owing to its slight severity and the renal complication attributed to cold when such is not the real cause In a series of 278 cases of war nephritis a history of a recent illness of a mild character such as a severe cold sore throat diarrhea etc was obtained in

10.4 per cent of the cases but in no less than 30 per cent the patients either gave a history of or presented signs and symptoms of bronchitis at the actual onset or in the early stages of the disease when admitted to hospital The marked frequency of bronchitis and respiratory symptoms in the early stages of nephritis was a striking clinical feature of these cases and some etiological significance might well be attached to it were it not for the fact that nephritis was practically unknown among the Indian troops although similar respiratory troubles only of much greater severity were prevalent amongst them There is thus no sufficient evidence to establish definitely an etiological relationship between nephritis and any antecedent illness

The bacteriological examination of the blood urine feces and throat in a series of one hundred cases failed to demonstrate any causal organism and it is of some interest that in ninety cases where the Wassermann reaction was tested the result was uniformly negative At the present time there is no complete evidence that the malady is the result of an infection although there is much to support this view

Morbid Anatomy of War Nephritis

Lesions are present in the glomeruli tubules and interstitial tissue resembling if not identical with those seen in the nephritis of civil life Hyaline degeneration and thrombosis are present in the glomerular vessels and proliferation of the glomerular epithelium may also occur The epithelium of the convoluted tubules shows marked changes the cells lose their striation stain imperfectly and are frequently hyaline and in many tubules the epithelium is shed Hemorrhages are found in and between the tubules and the interstitial tissue is swollen edematous and infiltrated with lymphocytes and polymorphs In the more severe and advanced cases the lesions in the kidney present a resemblance to those usually present in the so called large white kidney

Clinical Course of War Nephritis

In some cases the onset is sudden in others it is more or less gradual When sudden in onset the initial phenomenon is usually either dropsy or hematuria Shortness of breath general malaise headache or a more general failure of health with loss of appetite are the most constant initial symptoms in the cases of gradual onset these symptoms persist for some days or even

in some instances for a few weeks and then dropsy supervenes In exceptional instances the initial symptoms have been some severe uremic phenomena such as amaurosis or epileptiform fits These uremic symptoms usually suggest that the case in question is really an acute exacerbation of chronic disease or the sudden manifestation of a very advanced latent lesion, but such symptoms have occasionally occurred as initial manifestations in cases of primary acute nephritis

The cases of sudden onset characterized by marked hematuria form a very definite group inasmuch as the hematuria is not only well marked but moderate pyrexia is also present the temperature rising to 101 F or 10 F or even in some instances to 103 F Further such cases do not usually suffer from dropsy and if dropsy does occur it develops later when the hematuria and pyrexia have diminished or disappeared At the onset the urine contains a large quantity of blood and the disease may be ushered in with a slight rigor together with general aching pains in the limbs The blood in the urine usually diminishes rapidly in amount although the urine may be tinted red or contain microscopic blood for several weeks The pyrexia also subsides after a few days but one of the most characteristic features of the disease is a tendency to the occurrence of relapses each of which is accompanied with a return of marked hematuria and an elevation of temperature that may take the form of a single spike The clinical picture presented by these cases greatly resembles that described in civil practice as characteristic of renal embolism i e sudden pyrexia accompanied with marked hematuria there is however no evidence of embolism in these cases The temperature chart, if the relapses are repeated as well as transitory in their duration also presents certain resemblances to the temperature chart of trench fever and these renal cases may complain of limb pains and headache during the pyrexial period Cases of this type were seen by the writer in the initial outbreak of nephritis in the British troops in March 1915 prior at any rate to the recognition of trench fever as a clinical entity and further it is at least doubtful whether trench fever is ever followed by nephritis Although the most marked forms of this clinical variety of nephritis are sharply differentiated from the more usual dropsical variety of the malady there are intermediate cases where the hematuria is but slight and the pyrexia not above 100 F and where dropsy is present quite early in the course of the disease

In the great majority of cases of nephritis the initial symptoms are shortness of breath and dropsy and when the patient comes under observation pyrexia either is absent or very trivial in amount The edema is generally very obvious and not infrequently it is considerable in amount it is well marked in the tissues of the face loin scrotum and legs and is often if not

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generally, accompanied by ascites Ascites may be very marked and in a small number of cases has been so great as to require paracentesis Hydrothorax may also occur but is not so frequent as ascites The most marked characteristic of the dropsy is however the extraordinarily rapid manner in which it subsides in the great majority of cases and this affords one of the most striking differences in the clinical curve of war nephritis as compared with the experience of this disease in civil practice In most cases of war nephritis the edema disappears in from two to three weeks from the time when it was first detected and this is so even in cases of marked anasarca In the slighter forms of the affection it was not uncommon for the anasarca to disappear in a few days sometimes before the patient was admitted to a hospital on the lines of communication In some cases of a severe type the duration was more prolonged and resembled that familiar to physicians in civil hospitals The rapid subsidence of the dropsy was accompanied with a great increase in the flow of urine and a rapid diminution in the body weight. In the most severe forms of the disease pulmonary edema of the type common in renal disease and often affecting especially the upper lobes of the lung was not unusual and this might be well marked in cases with uremic manifestations and where anasarca and dropsy generally were not especially marked Dyspnea and bronchitis as already mentioned were also prominent symptoms at the onset and during the earlier stages of the disease and were not necessarily correlated with the degree of dropsy present

Headache was often a prominent symptom and sometimes an increasing intense headache was a prodromal symptom heralding the onset of an uremic attack Vomiting was not conspicuous except in grave cases and these formed but a small proportion of the total number Anemia was generally only present to a slight or moderate degree and it was exceptional for the patients to present the well known pallor and waxy appearance so characteristic of renal disease Uremic complications were not uncommon and a very remarkable feature of the clinical course of the malady was the frequency and severity of the epileptiform seizures that occurred Uremia generally took the form of sudden epileptiform seizures often repeated and general in their distribution although not uncommonly beginning locally Another remarkable feature was the small fatality of these severe uremic seizures and here again there was a notable difference between war nephritis and the nephritis of civil life This however may be dependent upon the fact that most of the civil cases are instances of chronic renal disease The uremic seizures were often heralded by the presence of severe and increasing headache and sometimes but by no means always by a sudden and considerable increase in the blood pressure It is remarkable seeing the frequency of epileptiform convulsions that the

other well known manifestations of uremia are uncommon thus amaurosis mania and coma apart from seizures have only occurred exceptionally and the well known uremic dyspnea or air hunger is very rare Retinal changes are rare in the earlier stages of the disease but retinitis similar to that seen in chronic renal disease has been described in some of the severe cases that ran a prolonged or chronic course

Urine in War Nephritis—The urine is usually diminished considerably in amount during the earlier period of the disease coincidentally with the occurrence of anasarca and the quantity usually falls to twenty ounces (600 c c) or less, in the twenty four hours in severe cases temporary complete suppression is not rare Blood is generally present in small amounts and as already mentioned there is a group of cases characterized by profuse hematuria The hematuria even when very slight is apt to be very persistent and to recur or increase in amount when the diet is increased and more especially when the patient first gets up Albuminuria varies greatly in amount from a mere trace only present for a few days to large amounts *e g* the urine becoming solid on boiling The albuminuria even in favorable cases is rather persistent and always lasts longer than the anasarca so that many cases are seen presenting only albuminuria and yet giving a history of having suffered from dropsy for a short period Hyaline granular and epithelial casts are usually present, together with numerous white corpuscles and frequently red cells and blood casts Renal cells transitional cells and squamous cells from the lower urinary tract are also found Fatty casts have been described by some observers but they are certainly uncommon

The blood pressure is almost always raised to a moderate degree but readings above 180 mm of mercury for the systolic pressure are rare and when present raise the suspicion of the existence of chronic renal disease The raised systolic pressure is coincident with the occurrence of edema and with the subsidence of the dropsy there is a fall in blood pressure This fall may take place either suddenly or gradually and the blood pressure may show marked diurnal variations Hydremia is usually present and generally occurs in association with the rise in blood pressure but variations in the degree of hydremia present may occur without corresponding changes in blood pressure Hydremia and dropsy are usually associated but hydremia may occur without dropsy and in exceptional cases dropsy may be present and marked when hydremia is either slight or absent (Dr Wesselow) In a considerable proportion of cases definite enlargement of the heart can be detected by the ordinary clinical methods similar to that known in cases of ordinary nephritis In war nephritis this enlargement is sometimes of temporary duration

The power of the kidney to excrete urea was often not greatly impaired and this is more especially true of that type of nephritis characterized by the presence of dropsy In other cases free from dropsy it may be greatly diminished and the amount of urea in the blood correspondingly increased The excretion of chlorides may be much diminished and the kidney may only slowly regain this power

Diagnosis of War Nephritis

This as a rule is not difficult but care must be taken to distinguish between acute nephritis and the sudden manifestations of chronic or latent renal disease Some difficulty may arise in separating cases of nephritis complicated by lobular pneumonia from cases of primary pulmonary disease complicated by nephritis Nephritis of a hemorrhagic type occurs as a complication of infected wounds and more especially as a sequel of streptococcal infections In rare instances a nephritis may be the initial manifestation of cerebrospinal meningitis and then difficulty may be experienced in distinguishing clinically between uremic and meningeal symptoms Lumbar puncture will usually afford direct and conclusive evidence

Prognosis in War Nephritis

The mortality of the disease is very low during the early acute stages notwithstanding the frequency and severity of the uremic seizures In a large series of cases observed in 1915 1916 the mortality was 0 4 per cent Subsequently there was an increased mortality and in 1916 it amounted to 0 93 per cent and in 1917 to 1 32 per cent This was partly dependent upon the fact that in the later years there were numerous cases where the nephritis was really not the primary disease but a complication in cases of primary lobular pneumonia of various types but owing to the severity of the renal lesions many of these cases were classified as cases of nephritis Some foreign statistics have yielded an even higher rate *i e* 2 2 per cent but these included cases that had become chronic Death may occur from uremia or from pulmonary edema rarely from cerebral hemorrhage and also rarely from inflammatory complications such as pneumonia pleurisy pericarditis These common inflammatory complications of nephritis are not often present in cases of war nephritis Relapses and recurrences are not infrequent especially if the soldier is allowed to return to duty prematurely

Treatment of War Nephritis

War nephritis requires treatment similar to that adopted in civil practice and usually these cases respond well and satisfactorily A restricted diet is indicated in the early and acute stages and especially when uremic symptoms are present but the mere presence of albuminuria or of dropsy in the later stages does not call for a diet unduly restricted in proteids Diuretics are sometimes useful in the dropsical cases and restriction of chlorides is also advisable

Sweating should be encouraged by the use of hot air baths and is often of great value Venesection is not only useful in the treatment of the uremic epileptiform seizures but if practised when prodromal symptoms such as headache and increasing blood pressure are present may prevent the occurrence of such seizures

Tonics and a moderately liberal diet should be given when the acute symptoms have subsided except when there is evidence of inability of the kidney to excrete urea Care should be taken that the period of convalescence is prolonged and that men are not put back to duty prematurely while the urine still affords evidence of the existence of a renal lesion

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CHAPTER XII A

CYSTITIS, PYELITIS AND PYELONEPHRITIS

By HENRY F HELMHOLZ AND EDWARD N COOK

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Definition—Cystitis pyelitis and pyelonephritis inflammation of the bladder of a renal pelvis and of the pelvis and parenchyma of a kidney respectively, all have the common finding of pus and bacteria in specimens of urine obtained from the bladder Without any of the more specific urological diagnostic procedures these three diseases can not be differentiated accurately one from the other The more severe and acute the infection the more likely is a kidney to be involved Thus, in a sense the diagnosis is pyuria with the localization of the infection many times in doubt particularly in the chronic infections In a child simple bacilluria at times may give the same acute febrile and general systemic symptoms as urinary infection with pyuria

HISTORY

For many years only those cases associated with stone and various obstructions in the urinary passages were recognized Simple inflamma

tion of the urinary passages was described first by Rayer in 1839 In children it was not until 1876 that the frequency of urinary infections was recognized by Huttenbrenner The discovery of bacteria in the late 1870's led to the identification of the various bacteria that cause urinary infection It was not until after the turn of the century that a cure was verified bacteriologically after discontinuance of medication It might be said that even at the present time the determination of the infecting organism and of its absence after clinical cure is not made as universally as it should be The ineffectiveness of certain drugs in the treatment of certain infections particularly the failure of the sulfonamides in *Streptococcus faecalis* infections is further reason for the importance of a determination of type of urinary infection

Etiology

Frequency —Pyogenic infections of the urinary passages are not of great frequency in the normal adult but they are encountered frequently in the male who has prostatic hypertrophy and obstruction and in the female during pregnancy In childhood they are encountered three to four times as often in the female as in the male As a complication of an acute infectious disease the typhoid bacillus appears more frequently in the urine than any other organism Anomalies of the urinary tract associated with obstruction predispose to infection and when present delay successful treatment

Bacteria —The gram-negative bacilli account for almost 80 per cent of the infections of the urinary passages These together with *Streptococcus faecalis* are probably of enteric origin while the other streptococci and staphylococci usually reach kidneys after they have invaded the blood stream The bacillus most commonly found is *Escherichia coli,* followed by *Aerobacter aerogenes, Proteus vulgaris* and *Pseudomonas aeruginosa* *Streptococcus faecalis* probably is followed most frequently by the staphylococci and hemolytic streptococci The frequency with which more than one type of organism is found in the urine is of significance as indicated by the isolation of several bacteria in culture and more recently, since the introduction of the sulfonamides by the disappearance of an apparently pure *Escherichia coli* infection and its replacement by pure cultures of *Streptococcus faecalis* Pyurias, which are sterile on ordinary culture, frequently are tuberculous in nature but

may be due to anerobic streptococci Actinomycosis may also be the etiological agent however it is seen rarely

Sterility of Normal Urine —The difficulty of obtaining a specimen of bladder urine free from contamination in the urethra makes it all the more remarkable how frequently when culturing 0 5 c c of urine one can obtain sterile specimens in the female by catheter and sterile specimens in the male by cleaning the penis and catching a specimen after allowing a few cubic centimeters to be passed How large a role in the sterility of the urethra the washing out by urine plays has not yet been determined Bacteria are not excreted by the kidneys but appear in the urine only after they have produced lesions in a kidney and broken through into the tubules or pelvis[3] It is known that in female infants during acute attacks of diarrhea with a decreased urinary output bacilluria is more common than in normal male infants

Mode of Infection —It is generally accepted that coccal infections of the urinary passages take place by way of the blood stream Coccal infections occur with about equal frequency in the male and the female while the gram negative infections are about three to four times more frequent in the female than in the male with the exception of the neonatal period when the incidence is the same At this time *Escherichia coli* is known to enter the blood stream frequently This discrepancy in incidence would seem to indicate that the gram negative bacillary infections probably occur by other than the hematogenous route and with the striking difference in the length of the urethra in the female as compared with the male makes it seem likely that infection is by ascent through the urethra into the bladder Clinically and pathologically it is impossible to distinguish between ascending and hematogenous infection in human beings Even in patients dying acutely within a few days the kidney is involved so diffusely that the mode of infection cannot be determined Experimentally pyelitis has been produced by intravenous and intracystic injection of *Escherichia coli*, and a definite differential pathological anatomical picture has been established for the rabbit[4] The spontaneous disease also has been studied pathologically and the findings resemble those of the ascending infection rather than those of the hematogenous infections[5] Furthermore for every 10 cases of cystic bacilluria or cystitis found in the cases of spontaneous urinary infection in the rabbit only a single case of bacilluria of the renal pelvis or pyelitis was found The involvement of the urinary passage was found in decreasing numbers as one passed from bladder to pelvis to renal substance This group of 67 rabbits 34 of which had bacilluria

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thickened membrane may be shown as leukoplakia In the proteus infections encrustative deposits may occur in bladder, ureters and pelves In the most severe forms ulceration and membranous changes are seen In overtreatment with methenamine the bladder may show tremendous edema hemorrhage and ulceration In pathological material obtained at necropsy the pelvis usually is filled with a milky exudate consisting of desquamated epithelium which in cases of mild pyelitis may represent the only layer that would have shown any inflammatory infiltration explaining to some extent why so frequently no changes are found in the renal pelvis

In its most acute form there is a diffuse leukocytic infiltration of the entire kidney with loss of function and rapid death of the patient This is usually the result of a severe infection and occlusion of the ureters The more common form the focal type of pyelonephritis may arise by hematogenous infection usually coccal in nature or by ascent from the pelvis to the parenchyma when it is bacillary in nature The kidney is enlarged edematous and covered with many small or a moderate number of raised yellowish areas surrounded by a hemorrhagic zone On section these areas usually are seen to be wedge shaped with the base at the surface The remarkable thing about these large abscesses involving as seen in later stages a large part of the renal parenchyma is that they do heal without drainage leaving a small sclerotic kidney with small practically normal areas of parenchyma next to completely scarred areas without any tubules and only a mass of hyaline glomeruli This tendency to healing probably can be explained best on the basis of the enormous blood supply that the kidneys have representing about a fourth of the cardiac output The abscesses in the cortex only rarely break through the renal capsule into the perinephric fat to produce a perinephric abscess which process also may be the result of direct infection of the perinephric fat from the blood stream

In the chronic forms of pyelonephritis the process may be the result of a single acute attack of pyelonephritis or of much less extensive repeated insults that produce the sclerotic shrunken kidneys with large pelvis and narrow layer of cortex The end result of the chronic recurring pyelonephritis may give a gross pathological picture as well as a clinical picture resembling chronic glomerulonephritis very closely In an experimental study of pyelonephritis it is the combination of infection and stasis that produces the severe disease Cortical abscesses have been found 18 hours after infection of an obstructed ureter To

and 33 of which had pyuria represents a more complete series of the various stages of urinary infection than are available anywhere else at present and tends to prove that infection of the renal pelvis is by ascent of the infection from the bladder within the lumen of the ureter by reflux rather than by way of the periureteric lymphatics If one can transfer the import of these findings in the rabbit to human pathology, it would appear that so-called gram negative renal infection is ascending rather than hematogenous in origin

Moreover, it is well known that in the absence of stasis it is extremely difficult to produce an infection of the bladder by the simple introduction of bacteria In order for infections to occur a lowered resistance of the mucosa must take place or marked pathogenicity of the invading bacteria must be assumed What the factors are in the uncomplicated case reducing the resistance of the vesical mucosa, we do not know

Infections of the pelvis can occur and persist for a long time without involvement of the renal parenchyma in the absence of stasis With obstruction of urinary outflow so rapid an involvement of the renal parenchyma can take place that the cortex is involved within 24 hours[6] The involvement of the renal parenchyma is by way of perivascular lymphatics by direct extension through the wall of the renal pelvis and by way of the blood vessels Ascent of infection through the collecting tubules was not observed The presence of mural thrombi within 24 hours after injection of bacteria into the completely obstructed pelvis makes the possibility of bacilluria from an ascending infection likely and does not necessarily predicate that the bacteria in the blood are the causative factors of the pyelonephritis They may be the result rather than the cause of pyelonephritis

Pathology

The changes observed in the pelvis ureters and bladder are essentially similar In the acute inflammation there is ordinarily redness and edema and occasionally, hemorrhage The inflammation may involve only the lining but may extend deeper, involving the muscle and fat tissue beneath and leading to thickening loss of elasticity of the ureters and loss of motor function In the chronic state the lining of the pelvis ureters and bladder may become thickened and granular It may show a cystic degeneration most commonly seen in the bladder, *cystitis* The

In chronic pyelonephritis the clinical picture is more variable than in the acute form In many instances the disease escapes recognition until it reaches an advanced stage A history of an acute attack followed by recurrent bouts of fever with headache lumbar pain dysuria and intermittent pyuria should arouse the examiner s suspicion of a renal infection In many cases recurrent difficulty of this type leads to little or no permanent renal damage However in others in which the pathological picture keeps increasing renal function becomes impaired and uremia develops as a terminal stage The disease here cannot be differentiated from chronic glomerulonephritis Such an end *result is a slow process and will occur rarely if the disease is recognized* and treated accurately

Chronic nonspecific unilateral pyelonephritis is an interesting clinical entity In many cases it is described as surgical pyelonephritis referring primarily to the fact that surgical removal of the kidney becomes necessary to bring about a cure It usually follows an attack of acute pyelonephritis in which both kidneys are involved One kidney gets well completely but infection persists in the other The diagnosis can be made only by urological study and recognition of the condition is important as occasionally hypertension may be related to unilateral renal disease

Renal abscess usually is of hematogenous origin although it has been known to occur with some ascending infections Small renal abscesses incidental to septicemia may not cause symptoms Pain in the loin associated with chills fever and renal tenderness on palpation may suggest renal abscess in the presence of an acute septic condition such as boil carbuncle or sore throat elsewhere in the body Renal carbuncle is the term applied to a coalescence of renal abscesses This condition may be extremely difficult to diagnose The urinary findings may be normal and only prolonged centrifugation may reveal any organisms usually staphylococci on staining the urinary sediment or on culture *If the renal infection extends into the perirenal tissues* producing perinephritis or perinephric abscess pain and swelling in the renal area may be noted and this pain may be exaggerated by a psoas spasm precipitated by flexion of the thigh

Perhaps the most common symptoms other than those associated *with difficulty in passing the urine are those related to obstruction along* the urinary passage Difficulty in passing the urine as evidenced by a small stream frequent urination and dribbling may be due to urethral stricture or prostatic obstruction When the obstruction occurs along

show the rapid healing in situ of even large renal abscesses, we want to cite the complete replacement by a syncytium of large polyblasts, phagocytosing polymorphonuclear leukocytes and debris in what looked like a pus filled abscess in the gross specimen in an eleven day old baby who had a urinary infection shortly after birth

Symptoms and Diagnosis

The symptoms associated with infections of the kidneys and bladder are variable not only in type but also in severity The symptoms of which the patient complains may be so universal that, unless the examiner is aware of the possibility of an infection of the urinary tract being present, he may miss the true condition

Localizing symptoms referable to the act of urination such as burning on urination frequent urination dysuria and nocturia, are noted commonly and usually are indicative of cystitis It is not noted commonly that this condition per se exists without being secondary to infection in the upper part of the urinary tract or some coexisting lesion in the bladder or vesical neck These local symptoms may be present in many instances when one is dealing with pyelonephritis Occasionally symptoms directly referable to the kidneys may be noted such as tenderness in the loin and pain in the costovertebral angle with or without anterior extension to the groin and genitalia When such symptoms are present it is not difficult to recognize infections in the urinary tract However in some cases there will be no localizing symptoms or signs the symptoms being more general in character as malaise fatigue and general ill feeling sometimes associated with attacks of chills and fever

Frequently a so called typical attack of acute pyelonephritis may begin with malaise fatigue chills and fever Headache is noted commonly Nausea and vomiting may be present This may go on for a period of days before any real localizing symptoms develop Pain in the costovertebral angle without extension along the ureter may develop and tenderness in this area may be elicited on palpation Symptoms referable to the lower part of the urinary tract may develop later such as frequent urination burning on urination and dysuria The finding of pus and bacteria in the urine with varying amounts of albumin is usual Microscopic hematuria usually is found but gross hematuria is found rarely

and grow in chains with their long axis in the axis of the chain The importance of this will be brought out later when treatment is discussed

If the examiner wishes to know the particular species present in any given case bacteriological cultures must be obtained The common gram negative bacilli are best differentiated on eosin methylene blue agar The specimens obtained for these examinations must be collected with aseptic technic

Following such a careful study of the urine if an infection is present, further urological study may or may not be indicated at the moment Certainly it is not necessary to advise a complete urological check in every such case However a long history of recurrent attacks of trouble severe symptoms colic chills and fever should suggest the need for more detailed study In all cases if the simple well recognized methods of treatment that are available today do not bring about a compete eradication of the infection a complete urological study must be carried out because it is known from past experience that in cases of uncomplicated infection of the urinary tract the percentage of complete cure is high As soon as a coexistent pathological entity is present such as stone tumor or obstruction the percentage of cure drops rapidly until this primary lesion is removed

In the simple uncomplicated cases the course of the disease is short if properly treated Care must be exercised when deciding on the con clusion of treatment All too often as a patient s symptoms subside medication will be discontinued and the patient pronounced cured The patient s well being is not an expression of cure, and it is necessary to determine this as well as the diagnosis by most carefully examining the urinary sediment again Here again it would be well to emphasize the fact that even after the pyuria disappears bacteria in small numbers may be present and their presence can be determined only by Gram s stain and culture of the urine This fact probably accounts for the frequent recurrent attacks noted so commonly in patients suffering with infections of the urinary tract without coexisting pathological changes

Treatment

The treatment of urinary infections consists in combating the general aspects of the infection fever lumbar pain nausea vomiting and diarrhea This requires the general measures usually employed in

the ureter or at the ureterovesical or ureteropelvic juncture the resulting back pressure along the urinary passage produces pain varying from mild discomfort to a severe colic With this may be attacks of chills and fever

The physical examination usually reveals little of note In some cases costovertebral tenderness may be elicited, in a few a mass the distended kidney may be felt Occasionally suprapubic or vesical tenderness on vaginal examination may be noted A palpable bladder above the symphysis indicates obstruction

The most important diagnostic sign is the finding of pus in the urine Such a simple diagnostic procedure as examining the urinary sediment will yield more useful information than all the rest of the history and physical examination The examination of the urinary sediment must be carried out properly First of all extreme care should be utilized in obtaining the specimen In the male examining the second portion of the urine passed is important, the first being discarded, as it may contain prostatic and urethral secretions, or it may be contaminated by those secretions associated with a redundant prepuce In the female a catheterized specimen must be used The only time when the findings in a voided specimen from a female are of true value is when they are entirely negative Only too often when a female patient is suspected of having a urinary infection the suspicion is considered to be confirmed because a voided specimen revealed pus in the urinary sediment which truly came from contaminating vaginal secretions rather than the bladder or kidneys

After a clean specimen has been satisfactorily obtained the urine should be centrifuged and the sediment examined first as a wet smear under the high dry objective of the microscope the number and kind of cellular elements present being determined Following this procedure, the smear should be thinned out, allowed to dry and then stained using any one of the numerous modifications of Gram's stain This slide then is examined under the oil immersion objective for any existing organisms Gram's stain divides the usual bacteria into two great groups bacilli and cocci and further subdivides them into gram-positive and gram negative organisms depending on their ability to retain or give up the initial stain used in this technic The particular species of organism cannot be recognized However one particular organism *Streptococcus faecalis*, can be identified frequently because while it is a gram-positive coccus the individual cocci are elliptical

ammoniac infection in which the pH of the urine usually is above 8 0 Alkalinization per se frequently gives relief from local vesical symptoms but has no effect on the infection The same relief is given when the urine is acidified and sterilized with mandelic acid

3 *Urinary antiseptics that require normally functioning kidneys* A damaged kidney is unable to excrete a urine of sufficiently low pH *5 5 to 5 0* to make possible the development of a bactericidal urine with the highest concentration of mandelic acid or beta oxybutyric acid that the kidney can excrete The same holds true for methenamine or mandelamine Even a severely damaged kidney can excrete the sulfonamides, penicillin and streptomycin in bactericidal concentrations

With regard to the use of urinary antiseptics the history should be a guide to the mode of procedure If the infection has followed a boil carbuncle or streptococcal infection and the symptoms clearly are those of renal involvement it is wise to begin with the administration of penicillin in dosage of 300 000 units daily Procaine penicillin is given usually because of its slow absorption and we feel that it should be supplemented by the oral administration of one of the sulfonamides If on the other hand the acute symptoms come on during pregnancy or in a man with prostatic obstruction or out of a clear sky it is well to begin with sulfonamide therapy Because of its rapidity of excretion it is advisable to begin with administration of sulfathiazole However various sulfonamides are now available and all are equally effective in most instances In our hands, we prefer sufathiazole sulfacetimide or gantrisin

The recently described administration of two sulfonamides may be of distinct advantage in reducing the danger of crystalluria The combined bactericidal effect will be doubled and yet the danger of renal damage will be merely that characteristic of half of the dosage given The relatively low dosage used in urinary infection hardly warrants this use of two sulfonamides The dose for any one of the sulfonamides rarely need be more than 2 grams daily when given orally The administration of the drug should be continued for a period of 7 to 10 days In the case of an acutely ill patient in which a sulfonamide is indicated but the patient cannot take the drug orally the sodium salt of either sulfathiazole or sulfadiazine may be given intravenously Fifty cubic centimeters of a 5 per cent solution of the sodium salt may be added to isotonic saline solution and given twice daily if necessary In general unless a great amount of fluid is being

the treatment of acute infection such as rest in bed, liquid diet and a large intake of fluids

The intake of fluids should be sufficient to maintain a daily output of from 2 5 to 3 liters of urine This may necessitate the intravenous administration of dextrose or saline solution The renal output of 3 liters acts to wash out the bacteria and their toxic products from the upper urinary passages and to reduce the number of the bacteria a factor which is of definite importance in the successful use of the sulfonamides It is questionable whether the alkalinization of the urine per se is of any advantage in the treatment of the infection It may, however, be of value in preventing crystalluria when using the sulfonamides

In the acute stage it is important to determine early whether the acute symptoms are caused by retention in either one or both of the kidneys due to stone stricture or other obstruction in the ureter, bladder or urethra Pain in the renal region with swelling of the kidney may indicate the side involved and necessitate drainage by ureteral catheterization

In the use of urinary antiseptics it must be realized that some act only under special conditions some better in an alkaline urine others only in a definitely acid urine some act well specifically on some bacteria and not on others and some act only when renal function is normal The rapidity with which organisms increase their resistance to the action of a drug is encountered especially in relation to streptomycin and greatly reduces its effectiveness

The *urinary antiseptics* can be divided into a number of groups

1 Urinary antiseptics that require a definite urinary acidity for action

a Methenamine requires a certain acidity usually a pH of 5 5 in order that, in the time the urine remains in the urinary passages the drug can be split sufficiently rapidly to maintain the concentration of formaldehyde at a level that is bactericidal

b The ketogenic diet[8], beta oxybutyric acid and mandelic acid require a pH of from 5 0 to 5 5 in order that from 0 5 to 1 per cent of the organic acid will act bactericidally It takes 10 times the concentration of the acid to act bactericidally at pH 6 0 than it does at pH 5 0

2 Urinary antiseptics that require an alkaline urine for most effective action

a Streptomycin acts with increasing effectiveness in the higher pH range This is seen most strikingly in its effectiveness in *Proteus*

infections of the urinary tract The most useful form in present use is procaine penicillin This is given daily in 300 000 unit doses intra muscularly When its administration is supplemented with one of the sulfonamides an existing infection of the urinary tract caused by the commonly found organisms with the exception of *Streptococcus faecalis*, usually will be eradicated A concentration of 3 units per cubic centimeter of urine usually is sufficient to control the infection Penicillin when given in this way is particularly useful in staphylococcic and bacillary infections

Streptomycin is the drug of choice in the treatment of infections associated with strongly alkaline urine as seen in cases of infection by urea splitting organisms[11] The higher the pH the more effective the drug Streptomycin has proved its greatest value in this group of cases which previously had been highly resistant to all drug treatment Doses of 500 000 to 750 000 units 0 5 to 0 75 c c are to be given intra muscularly four times a day Streptomycin should not be given by mouth as it is not absorbed from the intestinal canal In the use of streptomycin in other infections it is advisable to alkalinize the urine to a pH of 7 5 or above before beginning treatment and then to use the drug in the same dose as given previously Here too a result must be achieved quickly because of the rapidity with which the bacteria become resistant to the drug

Aureomycin[12, 13] is a new urinary antiseptic of considerable value It seems to be more potent than almost any other but its efficacy is diminished by any complicating pathological condition just as is that of the other chemotherapeutic agents At present its greatest value lies in combating infections due to *Aerobacter aerogenes and Streptococcus faecalis* The dosage most generally used is 32 mgm (gr ½) given 4 times daily for 6 days

Chloromycetin (chloramphenicol)[1, 12] is another new antiseptic which is similar in its usefulness to aureomycin The dosage of this drug is 0 5 gm given every 4 hours for 6 days

Inability to clean up the infection and its rapid return after sterilization should make one suspect that there is some abnormality of the urinary passage with associated stasis and a complete urological examination is indicated including determination of residual urine excretory *and retrograde urograms* cystoscopy and *ureteral catheterization* with culture and microscopic examination and stain

given the concentration of the sulfonamide in the urine can be figured at about 50 mgm per 100 c c for each gram of the drug given For children the drug can be given in a dose of 2 gm the first day and 1 gm in 0 25 gm doses four times a day thereafter

The effect of the sulfonamides is striking It is not at all unusual for the urine to be sterilized within 24 hours, even as early as 16 hours This does not mean of course that the infection has been cured in this length of time but it does indicate that the urine washing the mucous surface has been sterilized, and that, if the urine is kept sterile, the infected mucous membrane will heal in the course of a week or ten days It is, therefore, extremely important not to wait for a week to determine whether or not the urine is sterile but to make the determination after 72 hours or even after 48 hours If the urine is not sterile at the end of 96 hours it is not likely to be sterile at the end of a week It must be remembered that the great drawback in the use of the sulfonamides is their ineffectiveness against *Streptococcus faecalis*[10], and that a supposedly single infection with *Escherichia coli* may after 48 hours' treatment reveal a pure *Streptococcus faecalis* infection The use of the sulfonamides has brought to the attention of the clinician how frequently this streptococcus is associated with gram-negative bacillary infections If after a week or ten days the urine still is sterile, medication may be discontinued After an interval of 3 or 4 days to a week another culture of the urine should be taken If it too is sterile, the patient can be considered as cured If after a course of a week of sulfonamide treatment the infection persists it is well to try mandelic acid The urine must be definitely acid with a pH of 5 5 or below as tested with nitrazene paper Usually if a diet is given without citrus fruit or milk the usual dose of 8 to 12 gm of the ammonium or calcium salt of mandelic acid will render the urine sufficiently acid and with a bactericidal concentration of mandelic acid If the desired pH is not reached 1 to 1 5 gm of ammonium chloride or nitrate can be given 3 times a day after meals in addition Here too it is well to emphasize that it does not take more than 48 hours to sterilize the urine but administration of the drug must be continued for 7 to 10 days in the acute cases and from 2 to 3 weeks in the chronic cases and sterility of the urine must be checked 4 to 7 days after discontinuance of treatment Mandelic acid occasionally gives rise to minimal hematuria, which clears up rapidly when administration of the drug is discontinued

Penicillin has assumed an important role in the management of

CHAPTER XII A 1

RENAL NEOPLASMS

By LAURENCE F GREENE

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Since Grawitz in 1883 advanced the theory that many renal neoplasms arose from aberrant adrenal rests the pathogenesis of renal tumors has remained controversial This controversy has manifested itself in the many and varied classifications of renal neoplasms that have been advanced Some authors have based their classification on the probable site of origin of the neoplasm while others have relied chiefly on the histological picture[1-4] It is not germane to enter into the medical polemics of this problem The following simple classification has been employed at the Mayo Clinic

Classification of Renal Neoplasms

I Benign tumors
1 Adenoma
2 Fibroma
3 Lipoma
4 Angioma

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CHAPTER XII A-1

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Classification of Renal Neoplasms

I Benign tumors
  1 Adenoma
  2 Fibroma
  3 Lipoma
  4 Angioma

II Malignant tumors
1 Adenocarcinoma (hypernephroma)
2 Tumors of renal pelvis
3 Wilms tumor
4 Sarcoma

Benign tumors are seen at necropsy but rarely have clinical significance A distinction should be made between multiple adenomas which occur in arteriosclerotic kidneys and a solitary adenoma There is no evidence that the former become malignant The distinction between adenoma and adenocarcinoma is arbitrary inasmuch as the histological picture is similar It is believed that the solitary adenoma represents an early stage of the larger clinically malignant adenocarcinoma

Adenocarcinomas constitute 80 to 85 per cent of malignant renal neoplasms Included in this group are neoplasms which have been described as clear cell carcinoma granular cell carcinoma papillary carcinoma and tubular carcinoma Most of these histological patterns can be found on thorough inspection of every adenocarcinoma The term hypernephroma commonly is applied to this group of neoplasms in spite of the consensus that these tumors arise from renal tubular cells rather than from aberrant adrenal rests

Tumors of the renal pelvis account for 10 to 12 per cent of malignant renal neoplasms These neoplasms arise from the epithelium of the renal pelvis and calices and inasmuch as the renal pelvis ureter and bladder are lined with similar epithelium the behavior of tumors in these sites is analogous Wilms tumor (embryoma of the kidney), which constitutes 2 to 3 per cent of malignant renal neoplasms is a disease of infancy and early childhood Sarcoma is rare and accounts for 0 5 to 1 per cent of malignant renal neoplasms

Adenocarcinoma

Adenocarcinomas are of variable size but by the time they produce symptoms usually they are large They may be situated anywhere in the kidney but commonly involve the upper or lower pole The tumor usually is single and has an intact or broken capsule On cross section it is most frequently yellow in color and contains scattered hemorrhagic areas At times it may appear pale and exhibit cystic areas, calcium deposits may be present in areas of necrosis The microscopic picture is exceedingly variable, and different cell patterns may be found in a

single neoplasm Frequently large masses of clear cells resembling the epithelium of the renal tubules are found but the tubular structure usually is lost At times the component cells are small and granular with deeply staining nuclei More rarely the neoplasm may appear as papillary excrescences arising from the lining of a cyst

Distant metastasis occurs through the veins and direct extension may occur through the capsule and into the renal pelvis Clinically the lungs and bones are the most common sites of metastastic involvement Post mortem studies indicate that the liver adrenal glands opposite kidney brain and retroperitoneal lymph nodes are not infrequently involved

The characteristic triad of *symptoms* consists of gross hematuria pain and a tumor mass Unfortunately these symptoms appear late in the course of the disease Gross hematuria which is usually the first symptom to appear is delayed until the neoplasm has invaded the renal pelvis The hematuria is total in nature that is the urine is hemorrhagic at the onset of urination and continues so throughout the act Unfortunately the hematuria may be evanescent and days or months may pass between its appearances thus deluding the patient The pain is described as a dull ache in the flank but may be acute and severe when associated with the passage of blood clots Because of the protected position of the kidney under the ribs the detection of a mass may be difficult particularly if the neoplasm is not large and is situated in the upper pole of the kidney When palpable the mass is hard irregular nontender and moves with respiration

Occasionally the disease may manifest itself only by unexplained fever or anemia Rarely the first symptom may arise from a metastatic lesion of the lung bone or brain Such constitutional symptoms as weakness loss of weight and anorexia occur when the disease is far advanced

The definitive aids in the *diagnosis* of renal neoplasm are excretory urography cystoscopy and retrograde pyelography A plain roentgenogram may reveal enlargement or irregularity of the soft tissue outline of the kidney Fine mottled shadows caused by calcification are seen occasionally in association with adenocarcinomas The most characteristic pyelographic deformity is elongation and narrowing of one or several calices with abbreviation or disappearance of others The renal pelvis may be displaced medially or downward or may be completely obliterated Medial displacement of the upper portion of the ureter may occur When hemorrhage occurs cystoscopy will reveal blood

issuing from one ureteral orifice, in the absence of gross hematuria microscopic examination of the urine usually will disclose erythrocyturia Cystologic studies of the urine for malignant cells has yielded disappointing results

Prompt nephrectomy is the *operation* of choice for adenocarcinomas This must be preceded by the demonstration of life-sustaining ability of the opposite kidney and the absence of metastasis Nephrectomy usually is accomplished through a posterior lumbar incision, but occasionally a transperitoneal approach is employed in cases of extremely large neoplasms High voltage roentgen therapy is reserved for palliative treatment of inoperable neoplasms and for postoperative treatment the latter in the hope that it will devitalize any malignant cells that may have been left behind

The *prognosis* of adenocarcinomas of the kidney is poor If nephrectomy is inadvisable owing to distant metastasis or local extension a rapid fatal outcome is inevitable If nephrectomy can be performed the prognosis remains guarded Less than half the patients live three or more years after nephrectomy slightly more than a third of the patients live five or more years and approximately a fourth of the patients live ten or more years after nephrectomy

Tumors of the Renal Pelvis

Malignant neoplasms of the renal pelvis may be classified as follows (1) papillary carcinoma without infiltration (2) papillary carcinoma with infiltration (3) infiltrating carcinoma[3] In addition classification of the grade of malignancy of the neoplasm according to the histological method of Broders yields valuable prognostic information

Papillary carcinomas without infiltration are characterized by villous fronds projecting into the lumen of the pelvis Microscopic examination of the fronds discloses a central vascular stalk surrounded by cells composed of transitional epithelium and the absence of infiltration of the wall of the pelvis Papillary carcinoma with infiltration presents a similar picture except that infiltration has occurred into the muscle of the pelvis peripelvic tissue or kidney Infiltrating carcinomas extend into the renal pelvis but no villous projections into the lumen of the pelvis can be demonstrated Furthermore study of the degree of differentiation of the epithelial cells of the neoplasms which have been described permits classification into four grades of malignancy as de-

scribed by Broders Definite differentiation of the neoplastic cells into keratin or pearly bodies presents the picture of squamous cell carcinoma In approximately 15 per cent of the cases calcareous material is present in the kidney or ureter on the affected side

Papillary carcinomas of the renal pelvis with or without infiltration are frequently associated with similar tumors in the ureter or bladder or in both of these organs This involvement of the ureter and bladder can be explained best by the formation of independent multiple neoplastic growths rather than by spread of the neoplasm down the ureter via the lymphatic vessels or transplantation of malignant cells from one site to another It is suggested that the epithelium of the entire urinary tract is vulnerable to some cancerigenic agent

Papillary carcinoma without infiltration spreads by direct extension along the surface of the renal pelvis and ureter The infiltrating carcinomas extend locally into the renal parenchyma and by means of lymphatic and venous channels to the lungs liver adrenal glands lymph nodes peritoneum and bones

The *symptoms* of tumor of the renal pelvis are similar to those described for adenocarcinoma of the kidney These two types of neoplasms cannot be distinguished on the basis of the symptoms although hematuria is likely to be more frequent and more profuse in cases of tumor of the renal pelvis

Excretory urography cystoscopy and retrograde pyelography are employed in the attempt to establish a *diagnosis* of tumor of the renal pelvis It may be difficult or impossible to distinguish tumors of the renal pelvis from adenocarcinoma by roentgenographic means In many instances essentially similar roentgenographic deformities may be produced by either neoplasm If the tumor of the renal pelvis is papillary in nature and projects into the renal pelvis a tell tale filling defect may be seen in the pyelogram A ureterogram may likewise demonstrate a filling defect indicative of neoplasm of the ureter Cystoscopy may disclose papillary neoplasms situated in the vicinity of the ureteral orifice on the affected side if cystoscopy is performed during an attack of hematuria blood may be seen issuing from the ureteral orifice

Treatment consists of complete nephro ureterectomy or nephrectomy together with removal of the adjacent upper third of the ureter depending upon the presence or absence of papillary formation in the original neoplasm Since papillary neoplasms with or without infiltration are associated with neoplasms in the ureter or bladder or in both of these organs it is advisable to excise in addition to the kidney the

entire ureter and a cuff of the bladder around the corresponding ureteral orifice Associated vesical neoplasms are destroyed by electrocoagulation Periodic cystoscopic examinations should be performed to detect and destroy possible recurrences of the neoplasms Since tumors of the renal pelvis which are purely infiltrative in nature and have no papillary elements are usually not associated with neoplasm elsewhere in the urinary tract, nephrectomy with removal of the adjacent portion of the ureter usually is sufficient High voltage roentgen therapy is advised as an adjunct to surgical treatment

The *prognosis* is influenced by the histological nature of the neoplasm the degree of differentiation of the cells and the presence or absence of involvement of the renal vein and the lymphatics The prognosis is fairly good in instances in which the neoplasm is papillary without infiltration These lesions are usually of a low grade of malignancy and neoplastic involvement of the renal vein or lymphatics is absent 5 per cent of patients with such neoplasms live five or more years after operation The prognosis is poor in cases in which the neoplasm in addition to being papillary, is also infiltrative These lesions are usually of a higher grade of malignancy, and neoplastic involvement of the renal vein and lymphatics is common 16 per cent of patients with such neoplasms live five or more years after operation The outlook is practically hopeless in cases of infiltrating carcinoma of the renal pelvis This lesion is always of high grade malignancy, and neoplastic involvement of the renal vein and lymphatics is the rule Extensive metastasis occurs rapidly and widely Only 7 per cent of patients with infiltrating carcinoma of the renal pelvis live five or more years after operation

Wilms Tumor

Wilms' tumor (embryoma of the kidney) is a highly malignant tumor peculiar to infancy and early childhood The lesion is probably congenital in origin and usually is detected during the first three years of life its appearance in an adult is rare

The tumor is capsulated and rapidly grows to a large size, it may be solid or cystic with areas of hemorrhage and necrosis The histological appearance is that of undifferentiated or partially differentiated cells of epithelial or connective tissue origin In addition to epithelial cells smooth and striated muscle bone and cartilage may be found neoplastic invasion of the renal vein is common The neoplasm may spread

by local extension through the capsule and may metastasize by the veins or lymphatics to the lungs brain liver retroperitoneal lymph nodes and mediastinum

The most constant single *symptom* of Wilms tumor is the presence of an abdominal mass in an infant or child in the majority of cases the abdominal enlargement attracts the mother s attention Occasionally the first symptoms consist of vomiting abdominal pain and anorexia as a result of pressure by the neoplastic mass on adjacent organs Hematuria is not a common symptom

The *diagnosis* is suggested by the presence of an abdominal mass in an infant or child and is established by excretory urography or retrograde pyelography The roentgenographic appearance of the kidney is definitely abnormal and can only be described as bizarre no distortion is sufficiently characteristic to be positively indicative of Wilms tumor

The most widely accepted form of *therapy* consists in preoperative roentgen therapy which results in rapid decrease in the size of the neoplasm thereby facilitating nephrectomy Postoperative roentgen therapy is then administered Ladd advised immediate nephrectomy by a transperitoneal approach followed by roentgen therapy

Wilms tumors are extremely malignant and the *prognosis* is poor The most enthusiastic reports cite less than 25 per cent of five year cures In the vast majority of cases the tumor recurs within four months and death follows shortly thereafter The prognosis is better when the neoplasm occurs during the first year of life Gross hematuria and invasion of the renal vein are bad prognostic signs

SARCOMA

Sarcoma of the kidney is rare being encountered but once in every 30 000 necropsies The neoplasm may appear at any age but it is a disease not of children but of adults the peak incidence occurs in the sixth decade

Sarcomas usually are large and their surface is nodular and bosselated The color of the neoplasms ranges from dark brown to yellow The neoplasm may be solid but cystic changes hemorrhage and necrosis are common Fibrosarcoma is the type that occurs most frequently Other types of renal sarcoma expressed in the order of their frequency are myxosarcoma leiomyosarcoma rhabdomyosarcoma

and various combinations of these types[5] Sarcoma frequently invades the renal vein and extends into the perirenal fat and adjacent structures Distant metastasis occurs in the lungs, liver, peritoneum, adrenal glands and bones

An abdominal mass and colicky pain are the most frequent *symptoms* Hematuria occurs less frequently The *diagnosis* usually is established by means of roentgenography but inasmuch as there is no pyelographic deformity that is characteristic of sarcoma, the preoperative diagnosis usually is malignant neoplasm of the kidney

The *treatment* of choice is early radical removal of the affected kidney along with a generous amount of perirenal fat Roentgen therapy may be administered after operation in an effort to improve the end results which on the average will yield but 10 per cent of five year survivals

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CHAPTER XII A-2

HYDRONEPHROSIS

BY WM C QUINBY

The term hydronephrosis describes a condition of atrophy of the parenchyma of the kidney together with dilatation of its collecting spaces the calices and pelvis associated with some form of obstruction to the normal propulsion of urine away from the organ In its earlier stages at least this condition is a progressive one in which the substance of the kidney becomes more and more atrophic and the pelvis increasingly dilated until finally these structures are converted into a large irregular sac containing fluid similar to water in which are dissolved a few salts Thus the kidney is transformed into an organ whose function is either greatly diminished or destroyed

Though it is true that in most instances the condition which causes the obstruction to the outflow of urine from the kidney forms the underlying factor of which the hydronephrosis is the sequel still since the renal impairment often is the most serious aspect of the train of events set up by such an obstruction it is best to discuss the condition of hydronephrosis as an entity

A variety of conditions are found which cause interference with the normal mechanism of downward propulsion of urine from kidney to bladder with subsequent development of a hydronephrosis According to the location and nature of the obstructing factor we find that hydronephroses may be classified as unilateral or bilateral intermittent or persisting They may be divided also into those caused by congenital malformations and those of intercurrent or acquired type If the obstructive factor lies in the lower urinary segment such as urethra or bladder the hydronephrosis most often will be bilateral while the unilateral variety follows obstruction at some level of the upper segment the ureter and renal pelvis

A fact of great interest is that the kidney is the only one of the secreting glands of the body which responds to obstruction of its efferent duct by such an increase in size Other glands respond to obstruction of their efferent duct by cessation of function and early atrophy The kidney however continues to elaborate urine though in an imperfect manner to be sure and thus there is brought about the conversion of its pelvis into a large sac

Physiology

It has been shown that under normal physiological conditions urine reaches the outlet of the collecting tubules at the apex of each renal papilla under very low hydrostatic pressure. Indeed it may be that by the action of certain smooth muscle fibers which surround each papilla in a circular or spiral form there is caused a definite suction effect which would tend to lower this pressure even further. On reaching the pelvis the urine is propelled by peristalsis which, beginning in the calices, passes to the pelvis and thence travels down the ureter in a wave-like, somewhat irregular and intermittent fashion. On reaching the bladder the uretero-vesical valve is opened and the urine enters the bladder in spurts or jets.

Though a considerable volume of work has been done on the nerve supply of the ureter and on its pharmacology, the initiating factors of ureteral peristalsis still are not clearly understood. Its nerve supply apparently is of both sympathetic and parasympathetic origin, but it is not clear that either is entirely necessary for normal action. On the other hand the theory that ureteral peristalsis is caused by metabolic changes in the muscle fiber itself and thus is of myogenic origin has much in its favor. Support for this idea is furnished by the continued contractile waves which occur in the ureter after its removal from the body. But however this may be, the important point for the understanding of the mechanism of hydronephrosis is that for normal renal function there exists a delicate balance on the part of the collecting portions of the urinary tract by virtue of which an increase in the amount of urine produced by the kidney during diuresis will be removed immediately downward by increase in the rate of peristalsis so that a low pressure in the renal pelvis will be maintained constantly. A normally functioning pelvis and ureter is essential to proper renal function.

It is also important to note that the ureter is surrounded anatomically by a loose-meshed cellular connective tissue containing lymphatics and blood vessels. Though this tissue possesses a certain degree of plasticity, the conditions surrounding the ureter are far from as favorable as are those of the intestine, the peristalsis of which is made easy by the smoothness of the surrounding serosa. It follows that interference with normal ureteral peristalsis will be found to result from even slight degrees of pathological infiltration of its surrounding tissues. Such interference always tends in lesser or greater degree to stasis in the renal pelvis and the gradual formation of a hydronephrosis. Thus extra-ureteral as well as

intra ureteral factors must be considered in seeking the cause of a hydro nephrosis

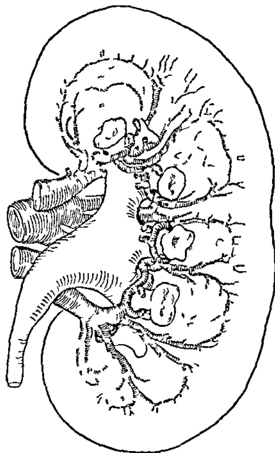


Fig 1 — Schematic sketch of distribution of renal veins in a circular arrangement close outside each minor calyx

Experimental Observations on the Formation of a Hydronephrosis

Earlier physiological observers in many and various experiments directed to the study of the secretion of urine measured the renal output by tying a cannula into the cut ureter Obstruction to outflow thus set up was found to result in the gradual increase of pressure to a point of between 50 to 70 mm Hg a point usually from 40 to 60 mm Hg

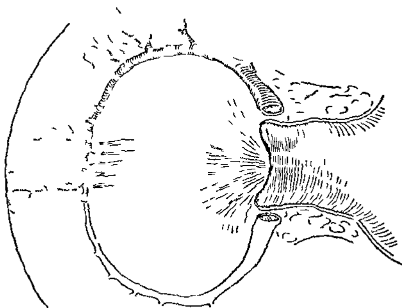
lower than the arterial blood pressure At this point the secretion of urine either ceased or if it continued was assumed to be taken up by tubular absorption In most of the experiments observation of this intrapelvic pressure was made only over several hours When the obstruction was allowed to last longer however it was found that the pressure always fell appreciably (Data concerning this subject are to be found in detail in the book of Cushny — The Secretion of the Urine Longmans Green and Co London 1917) These were acute experiments however and not directed to the question of hydronephrosis

To the extensive experimental work of Hinman and later of Fuchs we owe our present knowledge bearing on the method of formation of a hydronephrosis Two observations had been made earlier The first was that if the fluid pressure in the renal pelvis be raised continuously by injection through a cannula tied into the ureter eventually at a varying height of pressure the injected fluid appears in the flow from the renal vein The second observation was that after injection for retrograde pyelography of a fluid opaque to the x ray shadows appear occasionally in the film either in the form of brush like extensions beyond the minor calices or in irregular tracts extending outward from the hilum These undoubtedly represent extravasation of the injected medium beyond the normal limits of the pelvis and its divisions and at times are found even though pains be taken to prevent any significant increase of intrapelvic pressure by the injection

Further observations following these leads resulted in finding that the point of escape of the excess fluid on forcible dilatation of the renal pelvis was always at the fornix the point where the mucous membrane of the minor calyx is reflected over onto the surface of each papilla Here the limiting membrane lies very close to venous arcades which surround each papilla in a circular fashion Transfer of the distending fluid into the vein just at this point may occur after definite rupture of the mucous membrane or even may take place without actual rupture the fluid seeping between the interstices of the stretched single layer of epithelium Hinman has given this phenomenon the name of pyelo venous back flow Occasionally the injected fluid passed for a short distance into the collecting tubules of the papilla also but only in insignificant amounts

This demonstration of an exit point for the urine in instances of occlusion of the ureter goes far to explain the gradual formation of hydronephroses especially those of large size

In brief the events following a complete obstruction to the ureter seem to be as follows Immediately on closure of the ureter the pelvic pressure rises to the point where further formation of urine ceases



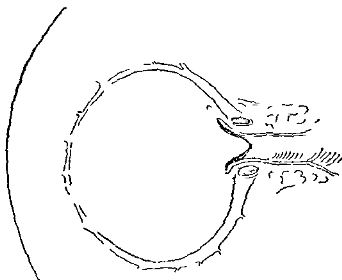


Fig 2 — Sketch showing area of fornix with its surrounding veins and cellular tissue under normal and under increased intrapelvic pres ure

There then occurs a gradual or sudden release of pressure through the membrane of the calyceal fornices with subsequent lowering of pressure

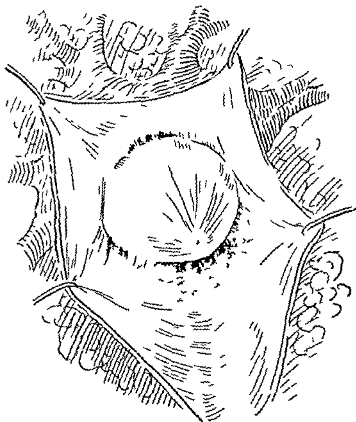


Fig 3 — Schema of enlarged papilla and fornix showing points of rupture where the covering of the papilla is reflected onto the wall of the pelvis

and resumption of formation of urine The pelvic wall in the meantime responds to the intermittent stretching at first by hypertrophy later by dilatation According to the height of intrapelvic pressure the renal

blood supply is impeded always considerably but in varying degrees This leads to atrophy of the renal parenchyma a process which always follows in irregular areas throughout the organ due to the earlier obliteration of some portions of the vascular tree than of others Eventually there is almost complete transformation of renal tissue into an atrophic and fibrotic shell surrounding the enlarged pelvis

This process of atrophy with hydronephrosis varies markedly in its rate of progression according to the prominence of one or another of its various factors Total and continuing obstruction such as results from the ligation of a ureter is followed by atrophy of the kidney after a relatively short time In such instances the hydronephrotic dilatation of the pelvis will have time to develop to only a moderate size In cases in which the obstructing factors act intermittently as for instance in the case of a movable calculus the degree of dilatation which may form before all urinary secretion has stopped is at times very large

The theories advanced by Fuchs are of considerable interest in regard to the significance of the fornix angle of the renal pelvis There seems to be no doubt that this area is significant from a pathological point of view as has been described above The further question arises as to whether under normal conditions this area of the pelvis may play a physiological role as well It has been suggested by Hinman that the relations here may be somewhat similar to those obtaining in the eye at the angle between the anterior chamber and cornea where there is direct drainage into the venous system without entrance of any blood into the non vascular structures Anatomical investigations of Fuchs have shown that the fornix is present only in mammals It has been argued that if fluid passes through the mucous membrane of this area of the pelvis then there must occur a definite rupture of tissue and that this of course is not a physiological process It has been pointed out however that this process need not go so far as to cause definite rupture but that under increasing pressure the transitional epithelial cells of the fornix are stretched becoming flatter and interstices appear between the cells Comparison is made between the cells here and those in the urinary bladder which when examined by microscope in the distended condition are seen as a layer of flat cells only one or two thick whereas when the bladder is collapsed the mucous membrane is at least four or five times as thick Comparative observation of the mucous membrane of the pelvis in the experimental animal under conditions of filling and ureteral ligation with those found under normal conditions show practically the same thing as in the bladder but these changes occur only in the region of the fornix not throughout the pelvis as a whole In fact in the micro

scopic sections it is sometimes hard to say whether the spaces between the cells merely are enlarged or whether the continuity actually is broken This is a transient condition however for as soon as the tension is diminished the stretching ceases It would seem that in many instances at least there is no direct rupture for microscopic examination after tension has been produced and then allowed to disappear shows no evidence of any reparative process which would be expected if there were actual rupture

Work on this general subject has been carried out also by MacKenzie and Hawthorne among others They found in their experiments that suspensions of ink could be traced into the intercellular areas of the fornix and from here into the perivascular spaces of the supporting structures of the kidney After injection of trypan blue without increasing the pelvic pressure Homuth found the blue seeping through the mucous membrane of the fornix thus suggesting that there may be a physiological tendency for diffusion of an intercellular character and that the main spot at which this occurs is this area alongside the papilla It thus becomes evident that there may be various grades between rupture on the one hand or intercellular diffusion on the other This assumes that in this circumscribed area of the mucous membrane there is increased permeability in a mechanical sense without a direct lesion of tissue

When considered from a developmental and comparative anatomical point of view reason is also found to ascribe significance to this portion of the kidney In the kidney of the human embryo at about two months groups of collecting tubules are found entering the minor calix but as yet there is no evidence of a fornix With the advent of the third month of intrauterine life changes take place first in the calices of the caudal end then in those of the cranial end The central collecting tubules remain while those of the periphery are absorbed and leave thus a groove around the collecting tubules which persists This groove is the original fornix By continued growth of the tubules toward the pelvis a papilla is formed

Fuchs suggests that the fornix area of the renal pelvis may be considered to have a regulatory function over the degree of filling of the pelvis It is an area lying between two independent systems Above is the renal parenchyma governed by factors influencing diuresis Below are the efferent passages with their mechanical function Attention is called to the conditions which theoretically may be assumed to be possible in which during a period of extreme distension of the bladder by urine there may coincide a period of abundant renal diuresis The argument runs somewhat as follows At the beginning of the retention of

urine the pelvis already is full If at this time a diuresis of 200 to 300 c c per hour or 100 to 150 c c per hour per kidney occurs this means that the contents of each pelvis must increase at the rate of about 2 5 c c per minute In other words during a retention of urine of only ten minutes duration the increase in the content of the renal pelvis during this time may be as much as 25 c c but being already filled the pelvis cannot accommodate this amount so the additional quantity is resorbed Although the wall of the pelvis and ureter can adapt themselves by increased peristalsis there must be some limit to this and there may be a situation set up in which more urine is delivered into the renal pelvis than can be propelled away from it This difference, it is assumed is cared for by resorption through the fornix It is pointed out further that in those patients bearing an infected urine but showing no fever if a Volhard test is undertaken there sometimes occurs a sharp rise of temperature during this test and that this fever may occur in spite of an inlying catheter in the bladder and without tenesmus or any other bladder phenomenon The fever may be accompanied by tenderness on pressure over one or both kidneys Such occurrence of fever of short duration also is seen frequently in patients whose bladders have been on drainage by a suprapubic tube after the tube is removed and following immediately the first or second voluntary urination That such fever is due to absorption of the products of infection from the urinary tract through the kidney cannot be doubted and all evidence at hand goes to show that it occurs by this process of reflux through the fornix

In summary the process of resorption through the fornix may be considered to have a physiological as well as a pathological significance, for it may occur without direct rupture but only through the intercellular spaces when the intrapelvic pressure is elevated From a developmental point of view it is suggested that the fornices are a specialized area which may have some function Certainly the assumption of such a mechanism is necessary in order to explain the formation of a hydronephrosis

Pathology

The appearance of the hydronephrotic kidney will vary of course according to the completeness of the obstructing factor and the length of time during which it has been effective In the early stages of the condition the kidney itself shows only slight thinning of the parenchyma together with an increase in the cubic capacity of the calices and pelvis of only moderate amount But with increasing duration of the obstruction there follows disappearance of tubules and later of glomeruli in many

areas due to interference with their blood supply The wall of the pelvis which at first shows hypertrophy of the smooth muscle fibers as a result of increased efforts to expel the urine downward later becomes dilated and thinned out with loss of elastic fibers and fragmentation of cells replaced by connective tissue The interstitial structures of the kidney resist dilatation longer than does the parenchyma and so remain as fibrous septa in which run the attenuated arteries and veins Thus the surface of the kidney is thrown into bosses consisting of rounded elevations with depressions between somewhat reminiscent of the normal lobulations of the fetal kidney At the same time the pelvis becomes more markedly dilated so that it protrudes as a globular swelling tensely filled with urine on which the kidney sits in a cap like fashion This increase in size occasionally may reach a degree so great that the kidney comes to form a large tumor filling the flank and possibly reaching the midline of the abdomen and descending well below the iliac crest

Symptoms

The symptoms caused by a hydronephrosis depend in the first instance on the suddenness and completeness of occlusion of the ureter of the involved kidney and will therefore be found to vary from no symptoms at all to those of severe colic with nausea vomiting and general prostration as in the classical Dietl s crisis Though in some cases the cessation of pain is followed by the passage of an unusually large amount of urine this point often is not noted or absent At times especially during the attack of pain the distended kidney forms a readily palpable mass in the loin But this may be obscured by spasm of the overlying muscles of the abdominal wall In those cases in which the obstructive factor is less sudden in its operation there may be complaint of a heavy or dragging feeling in the loin Others experience a slight swelling which may be more or less tender at varying times Fever and chills with purulent urine usually connote infection as a complication Hematuria does not occur in the uncomplicated case

It is important to realize always that the underlying condition which causes the hydronephrosis may be the cause of whatever symptoms are presented while the damaged kidney remains entirely in the background

Diagnosis

It is best that the steps of urological diagnosis be undertaken in a routine way in order that no aspect of the conditions present be over

looked A history general physical examination including palpation by vagina and by rectum is followed by analysis of the urine In women always this should be made of a specimen drawn by sterile catheter In men it is always wise to observe the act of micturition as regards its force and character One proceeds then to the special urological portion of the examination the first step of which usually should be to make a plain x ray film According to the suggestions thus far obtained the next step may be the making of the so called excretory urogram For this some one of the shadow casting compounds is injected in proper amount into an arm vein following which x ray films are made at intervals of 5 15 and 30 minutes When positive information is obtained from such films it is of much importance but negative evidence frequently is nearly valueless Investigation of the urethra and bladder next is undertaken by cystoscope This is followed by the collection of urine from each kidney by means of the ureteral catheter and the subsequent study of the function of each kidney As a final step contrast fluid is injected into the renal pelvis and a pyelogram made

When properly interpreted the evidence to be had by means of the ureteral catheter is very enlightening A suggestion that hydronephrosis is present often will be had from observation of the initial flow of urine through the catheter Under normal circumstances urine is ejected from the catheter in a series of a few drops with longer or shorter intermissions according to the degree of ureteral and pelvic peristalsis If the tip of the catheter be in a pool of urine however as when the pelvis is dilated the flow through it will be continuous Another method by which increased capacity of the pelvis may be demonstrated is by forcible suction applied to the catheter by a syringe If on withdrawing the piston the syringe fills quickly and readily a capacity of the pelvis greater than normal is suggested The quality of the urine coming from each kidney then should be observed and the presence or absence of infection noted For the determination of renal function the best test because of its ease of performance and reliability is the estimation of the ability of the kidney to excrete phenolsulphonephthalein A normal kidney excretes about 1 per cent per minute under conditions of adequate diuresis Comparative function usually is studied in specimens collected during a fifteen minute period after noting the appearance time of the drug A final step is the making of the pyelogram For this the substance chosen should be injected through the catheter slowly and in an amount not exceeding 10 c c unless the pelvis has been shown to be dilated by the earlier test The average capacity of the renal pelvis being taken as about 15 c c over-distension thus is avoided But should pain be

caused before the full amount of 10 c c has been injected filling should be stopped at once and after an x ray film has been exposed the fluid should be aspirated by suction It is our experience that by the use of the newer and less irritating substances such as hippuran carefully administered as outlined one is able to avoid the rather severe renal colic which frequently followed pyelography in earlier days In some instances further information can be had by making two x ray films taken stereoscopically as well as by taking films of the injected pelvis after the position of the patient has been changed from the horizontal to the sitting The modern cystoscopic table makes possible all these measures quickly and easily

Clinical Varieties of Hydronephrosis

For purposes of clear discussion the various outstanding forms of hydronephrosis are best considered under the following headings

A Physiological hydronephrosis that accompanying pregnancy

B Congenital group accompanying

1 Valves of urethra in the male
2 Anomaly of lower end of ureter
3 Anomaly of the renal blood vessels
4 Anomaly of the kidney either in size form or position

C Acquired group accompanying

1 Urinary stone
2 Neoplasms of bladder and uterus
3 Infections without the urinary tract

Hydronephrosis Accompanying Pregnancy

The simplest type of hydronephrosis is that which constantly is associated with pregnancy In this state with the increasing size of the uterus there occur also physiological changes in the ureter which lead to a definite dilatation and atony of it and of the renal pelvis Under normal conditions these changes are not of sufficient degree to cause any significant impediment to renal function and after parturition the urinary passages return to their former size Pressure on the ureter as it crosses the brim of the bony pelvis especially on the right side is considered to be one reason for such hydronephrosis besides which certain hypertrophic changes have been demonstrated to take place in the lower or pelvic segment of the ureter possibly a sequel of hormonal influence

Whatever the cause may be it is shown clearly by pyelography made

during the course of normal pregnancies by either the retrograde or by the intravenous method that such moderate hydronephroses do occur that they are repaired at the termination of the pregnancy and that they are not of sufficient duration to damage the kidney The real significance of such mild obstruction lies in its offering a more favorable opportunity than normal for the growth of bacteria should infection supervene Pyelitis during pregnancy thus becomes an important complication of this state and one which as is well known may be unusually severe so much so at times as to necessitate termination of the pregnancy if the woman is to be saved from a chronic pyelonephritis afterward A still further important consideration in this regard is that once severely infected the hydronephrotic kidney can regain sterility only with difficulty, even though the uterus be emptied for after such a bacterial invasion the collecting portions of the kidney and the ureter do not regain their normal size and function Evidently the inflammatory reaction in the walls of these structures by destruction of elastic fibers and cellular infiltration cripples their normal peristaltic action

Ovarian cysts or uterine fibromyomata when of large size occasionally are found to cause hydronephroses in a way similar to those associated with the pregnant uterus

As a rule unless infection supervenes there are no symptoms caused by the dilated kidney during pregnancy However frequent observation of the urine during the prenatal care of the pregnant woman should be undertaken always with respect to its sterility just as much as in regard to its other evidences of normal renal function If pus or bacteria are present in the specimen drawn by catheter immediate measures should be taken to fight such infection before it has become overwhelming

Valve Formation in the Posterior Urethra

In this anomaly which occurs only in the male abnormal cusps or adhesions are present in various forms at the level of the verumontanum The impediment to urination thus caused may be extreme moderate or slight according to the degree of obstruction Distension of the bladder with breakdown of the uretero vesical valve mechanism is followed by bilateral hydro ureter and hydronephrosis Infection by the colon bacillus usually appears at an early date which of course adds to the burden already placed on the kidneys

The typical case is seen in an infant or youngster who has been noticed to urinate with difficulty Often enuresis is present due to over flow from a bladder distended to its maximum In the advanced case

the child is poorly nourished and has a protuberant abdomen in which not only the bladder can be seen and felt but also the kidneys and sometimes the ureters as well When renal damage of so marked degree as this has been allowed to occur death from uremia and uro sepsis is imminent and usually unavoidable Since this whole train of events can be relieved easily by a simple excision of the obstructing valves either by transurethral or suprapubic operation it is always a great pity that the diagnosis is not made much earlier than is the case at present Injection by vein of some one of the substances used for urography followed by x ray will outline the urinary passages and bladder outlet as well giving a clear cut picture of the area of obstruction and the condition of the kidneys

Case Report —A boy of 12 years presented the following history At 8 weeks of age he was circumcised When 9 months old the urine was noted to be turbid and to cause much irritation of the external genitalia When 2½ years old inspissated pus was seen frequently at the meatus This continued to make urination difficult so that the stream was described by the mother as no larger than a hair At 4 years of age an attack of acute retention of urine necessitated etherization and the passage of an instrument which withdrew a large amount of foul smelling urine After this urine was passed more easily Subsequently the urine has always contained pus and albumen and the boy has been treated by dietary regimen for nephritis

Examination showed a bilateral hydro ureter and hydronephrosis The kidneys had entirely lost power to concentrate urine and the phthalein test showed marked delay in excretion The blood urea nitrogen estimation still was normal The obstructing valves were excised by operation with relief but it is extremely doubtful if the long standing pyelonephritis and ureteral damage can be much benefited

Developmental Anomalies of the Lower End of the Ureter

The anomaly of the lower end of the ureter which is associated constantly with hydronephrosis is that of congenital stricture This may be bilateral and of such severe grade that death occurs shortly after birth Less marked instances frequently unilateral are seen in which the narrowing is situated at the extreme vesical end of the ureter and is restricted almost entirely to the mucosal and submucosal layers By pressure from above there occurs dilatation so that there forms a protrusion into the bladder which has been called cystic dilatation of the lower end of the ureter or ureterocele As observed through the cys

toscope at each ureteral efflux the dilated mucosa swells in balloon fashion the opening through it into the cavity of the bladder being very tiny The size of this cyst like swelling may be so large at times as to appear at the urinary meatus in women

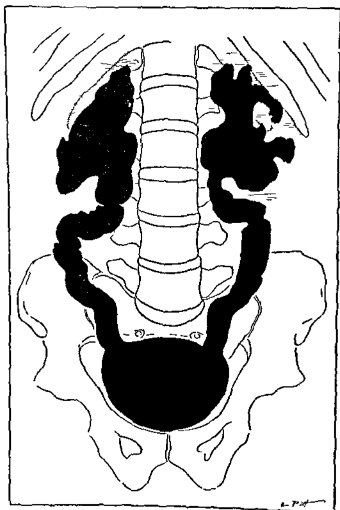


Fig 4 — Cysto-uretero pyelogram of patient having valvular obstruction in the posterior urethra Extreme dilatation of both ureters and renal pelves with resulting destruction of renal parenchyma is evident.

As a rule no symptoms are caused until infection or infection with stone formation has taken place Transvesical excision of the redundant ballooned out mucosa easily cures the condition

Case Report A woman of 38 complained of occasional attacks of

pain on the right side of the abdomen just below the costal margin associated with moderate fever and pus in the urine Examination showed a reduplication of the ureter on the right side accompanied by a ureterocele of the ureter draining the upper pelvis This also had become

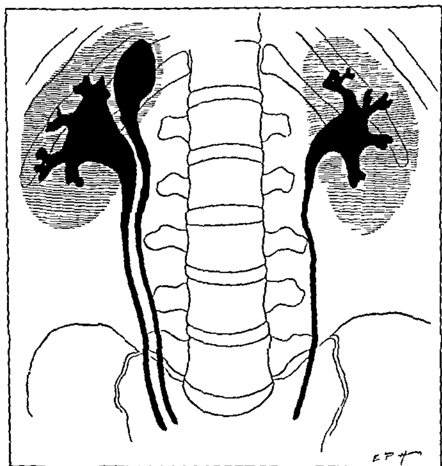


FIG 5 — Pyelogram of patient showing hydronephrosis in upper pelvis drained by a reduplicated ureter the vesical end of which was obstructed by a ureterocele

moderately dilated and was the site of a chronic bacillary infection The opening in the ureterocele was enlarged

During the ensuing ten years the patient has been free from further attacks of pain and has shown no urinary infection A urogram however finds that there is still present a moderate hydronephrosis which causes

no symptoms because the drainage through the ureter below has been made adequate

Other ureteral anomalies such as duplication or insertion of the lower end outside of the bladder while they may cause hydronephrosis frequently do not do so

Vascular Anomalies of the Kidney

A very important type of hydronephrosis rather frequently seen is one of which the cause lies in some form of irregularity of the renal blood supply Deviations from the normal type of one renal artery and one renal vein are known to be very common but only in an occasional instance does a hydronephrosis result Such irregularities in the development of the renal vascular supply follow faulty absorption of some one or other of the multiple vessels which serve the kidney during its ascent from the pelvis to the loin during embryological growth Normally these vessels have disappeared at birth leaving the single renal artery and vein One or another may persist however usually as an accessory artery entering the renal substance at its upper or lower pole independent of the hilus vessels At times there is no definite single renal artery the kidney being supplied by several polar vessels Anomalous persistence of veins is less common or at least is less often associated with hydronephrosis

Of these aberrant arteries the one supplying the lower pole of the kidney is that one which is found to lie in such position as to interfere with the lower aspect of the pelvis at its junction with the ureter The central origin of such vessels may be either from an early division of the renal artery or from the aorta lower down or even from the iliac artery whence it takes an ascending course to reach the kidney

Close apposition of such an aberrant artery to the wall of the pelvis at its outlet or to the uppermost point of the ureter always is present in cases showing hydronephrosis Evidently the manner of action of a vessel so placed is to interfere with the normal transmission of the peristaltic wave from pelvis downward to the ureter Certainly in the beginning interference is not sufficient to cause a mechanical obstruction of the ureteral lumen There is no inflammatory element present and no anomaly of the pelvic outlet such as stricture or valve With gradual increase in the size of the pelvis above the vessel however a bulging mass is produced which when sufficiently large does definitely angulate the ureter The hydronephrosis increases in size to the point at which occlusion becomes complete thus bringing on an acute attack of colic

It is a characteristic of this condition to develop slowly so that the hydronephrosis does not become manifest as a rule till sometime during the second decade of life The clinical picture therefore is one definitely related to the period of late childhood and adolescence Even though the patient may be older a careful history usually will place the first attack of colic at this age The attacks vary much in frequency but with the passage of time they increase in severity and the time between attacks becomes shorter At times the history will show the condition to have been present for two or three years At the height of the attack nausea and vomiting are frequent so that the youngster is often thought to have an upset stomach from some indiscretion of diet Fever is rare and examination of the urine finds it normal or containing only a little albumen The diagnosis is made clear by the demonstration of a hydronephrosis by pyelography easily carried out by the intravenous method

There are two prominent reasons why this especial type of hydronephrosis should be kept constantly in mind by the pediatrician and clinician first because the symptoms fall at a period of life when the individual is young and usually otherwise healthy and second because with prompt diagnosis at a time before the kidney has been destroyed a plastic operation will relieve the condition and cure the patient Recent examination of six patients over ten years after such plastic operation found that all had been relieved entirely from further attacks and that with one exception the function of the involved kidney was adequate in all

Case Report — A 14 year old school girl was seen on March 9 1922 complaining of attacks of pain on the left side of the abdomen during the previous three years The pain occurred with considerable frequency at times as often as every other week It appeared as a rule rather suddenly toward the end of the day and as it increased in severity was followed by nausea and vomiting An appendectomy performed 7 months before had not influenced these attacks of colic The catamenia had been normal and bore no time relation to the pain She was more comfortable when lying and sleeping on the left side In the intervals between these crises she felt entirely well

Physical examination found a well developed and well nourished girl with normal temperature The only abnormality was a moderate sensitiveness on palpation in the region of the left kidney The urine was normal the hemoglobin 90 per cent the white blood cells 10 400 Cystoscopy showed a normal bladder The right kidney excreted 17 per cent phenolsulphonephthalein in 15 minutes the left only 2 per cent A pyelogram found a left hydronephrosis of moderate size

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The Anomalies of the Kidney

Anomalies of the kidney itself involving its position size or shape, such as the horseshoe kidney the ectopic kidney and the con

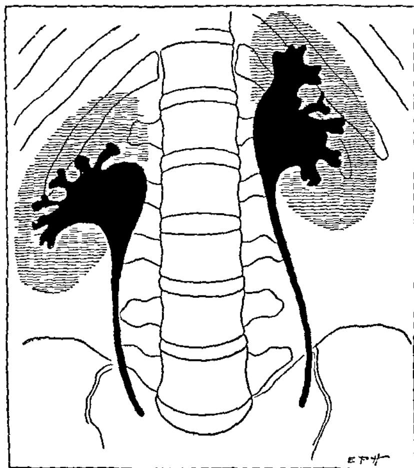


FIG 7 — Sketch of intravenous pyelogram made 15 years after operation for the hydronephrosis illustrated in Figure 6

glomerate kidney are associated only occasionally with hydronephrosis of any significant size In the majority of these abnormalities symptoms are not caused by retention but by the advent of infection or possibly by the formation of calculus

At operation an aberrant artery ran across the uretero pelvic junction to the lower pole of the kidney The ureter was divided and reimplanted into another area of the dilated pelvis

The patient was examined again on March 15 1937 fifteen years

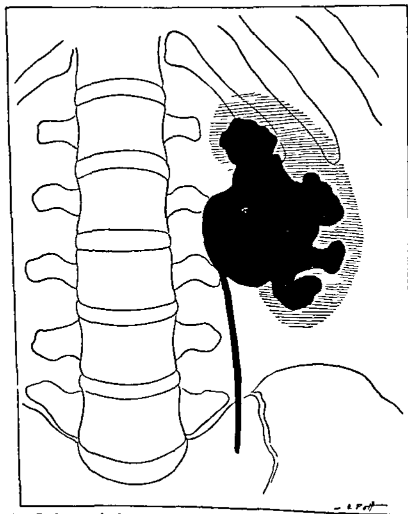


Fig 6 — Pyelogram of a hydronephrosis caused by an aberrant artery to the lower pole of the kidney

later She had been entirely well in the interval and had been through normal pregnancy The urine was normal Excretory urograms showed filling of each pelvis at 5 minutes after injection persisting till 30 minutes Each pelvis appeared slightly larger than normal the left more so than the right The emptying time of each was normal

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Acquired Hydronephrosis

In those cases making up the group of acquired hydronephroses the symptoms caused by the lesion or disease of which the obstructed kidney is the sequel usually dominate the clinical picture In fact when symptoms and signs are outstanding it is very easy to overlook the progressive and silent destruction of the kidney above This is not the case in calculous disease however for here the colic doubtless is due to the obstructive overdistension of the renal pelvis in greater degree than it is to pain set up by the movement of the stone downward in the ureter Instances of so called silent stone are met occasionally in which marked hydronephrotic changes of the kidney have appeared before the advent of eventual obstruction leads to medical investigation Taken as a whole however in cases of calculous disease it is the destructive effect of secondary infection rather than mechanical blocking of the kidney which forms the greater danger for the patient

Bladder neoplasms as well as those of the uterine cervix almost invariably are associated with hydronephrosis of either one or both kidneys when such tumors have reached a size sufficient to interfere with the lower end of either ureter So general is this renal impairment in either of these forms of cancer that the immediate cause of death is seldom the widespread malignant metastases and cachexia seen in other forms of neoplasm but rather due to renal impairment by hydronephrosis and urosepsis As mentioned above such renal impairment often is insidious and not always realized until looked for Such early involvement of the ureter is explained by the predilection of vesical tumors to be situated in the lower segment of the bladder near one or the other ureteral opening on the one hand and by the tendency of cervical carcinoma to extend early into the area of the broad ligament on the other

A final type of hydronephrosis is that which follows interference with ureteral function by inflammations external to it The commoner type of such condition is that caused by chronic pelvic suppuration in women A less well recognized cause is that seen in the lymphadenopathy of tabes mesenterica In either of these ailments it is important to evaluate the kidney by pyelography Occasionally operative intervention to free the ureter may be demanded

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CHAPTER XII—B

NEPHROLITHIASIS

By J. M. Hayman, Jr.

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Introduction

Definition.—Nephrolithiasis may be defined as concretions of crystalline urinary constituents usually mixed with organic matter which commonly develop in the calices or pelvis of the kidney. A stone may remain in the kidney or pelvis as a renal calculus or pass into the ureter to become a ureteral calculus or become arrested in the bladder as a vesical calculus. A small stone reaching the bladder from the upper urinary tract usually is passed through the urethra, but if retained in the bladder it may gradually increase markedly in size. Rarely, particularly in the presence of stasis and infection, a stone may form primarily in the ureter, bladder or urethra. Regardless of the point of origin, the general composition and essential characteristics of urinary stones are identical. Aside from the discomfort of attacks of pain, unless passed or removed, renal stones are prone to cause grave symptoms and irreparable destruction of renal tissue due to the frequent complication of infection and obstruction. Procrastination on the part of patients whose stones are not too troublesome, delay in diagnosis because they are symptomless, missed diagnoses or mismanagement led Hunt[1] some

CHAPTFR \II — B

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years ago to state his belief that one third of all patients with renal stone lose a kidney by destruction or nephrectomy

Incidence of Renal Calculi

The incidence of renal calculus is not uniform throughout the world Definite stone areas have been described in India, China[3] Mesopotamia, England France Russia and southern California Stone is relatively uncommon in such dairy farming countries as Switzerland Denmark and Ireland where the population enjoys a well balanced and mixed diet It is most prevalent among people living on an incomplete diet, particularly where cereals form the staple food Renal stone is much more common in hot countries than in cold and in dry tropics than in wet The difference is more probably due to dietary factors than to the climate itself Likewise, the apparent racial frequency of stone among Hindus Arabs and Southern Chinese only persists in their descendants when they carry on their tribal habits of living and continue to subsist on the same diet Vermooten[4] found no stones among the South African negroes in Johannesburg who eat a simple diet, which is low in calcium, has an acid ash and is rich in vitamin A At the same time stone was present in 1 460 hospital admissions among the white population Urinary stone also is rare among the Esquimaux The consensus of opinion at the present time is that the formation of stone is less a question of climate and race than of food produced in that climate and eaten by that race

Renal calculus occurs at all ages It is more common in children in parts of the world where their diet is presumably deficient as in India China and Syria[5], while in England and the United States it occurs most commonly between the ages of 30 and 50 But it must be remembered that stones may grow very slowly or be so located that they cause no symptoms and therefore may have been present for many years before they are discovered Usually it is stated that stone is more common in the male but this applies only to vesical calculi for there is little difference in the incidence of stone in the kidney and ureter in the two sexes Severely infected calculi however, are much more frequent in females Both kidneys are affected about equally they are bilateral in 10 to 20 per cent of cases and multiple in 40 per cent Bilateral *multiple stones* frequently are associated with infection and obstruction The only form of lithiasis which is definitely familial is cystine calculi associated with cystinuria

Etiology

In spite of a vast amount of experimental work and clinical observation no single explanation has been developed to account for the formation of urinary

calculi Viewed as a phenomenon of the precipitation of substances from solution the formation of concretions in the urinary tract just as in the gallbladder prostate or elsewhere in the body must find its ultimate explanation in the theories of the physical chemist Several concurrent factors probably are required always and it is probable that these differ with different types of stones as well as in importance in different individuals

Colloid Crystalloid Imbalance

The theory that the formation of renal calculi was due to a disturbance of colloid crystalloid balance in the urine was put forward many years ago It holds that urine is a supersaturated solution in which salts and organic solutes are held in solution by the presence of protective colloids Any increase in the concentration of crystalloids or decrease in the concentration of protective colloid or alteration in its character will disturb the normal delicate balance leading to the precipitation of crystalloids and their agglomeration into a stone Keyser[6] was able to produce aseptic calcium oxalate calculi in the renal tubules of rabbits and dogs by injecting butyl oxalate subcutaneously On microscopic examination he found that as the oxaluria increased the normal octahedral crystals gave way to tabloid dumb bell and spheroidal types which showed a greater tendency to fuse with the formation of small calcium oxalate concretions It is supposed that infection a metabolic abnormality or anything which disturbs the colloid crystalloid equilibrium of the urine results in the precipitation of urinary salts and that this precipitate even though it be very slight may act as a nucleus for the formation of a stone

Newcomb[7] however points out that urine contains many other substances besides colloids which may affect the solubility of sparsely soluble substances Uric acid for example will dissolve more readily in the presence of phosphates He was unable to repeat Joly s[3] experiments on the precipitation of urinary salts on dialysis but found that if the pH was unchanged the urinary salts stayed in solution as well without colloid as with it He believes that while normal urine undoubtedly contains colloids it is very doubtful if these have any considerable influence on the precipitation of such constituents as ordinarily go to form urinary calculi Moreover crystals of precipitated salts such as calcium oxalate phosphates and uric acid may be passed in the urine over long periods of time and seem to have little relation to stone formation

Vitamin A Deficiency

Osborne Mendel and Ferry[8] in 1917 reported phosphatic calculi in the urinary tract of 9 3 per cent of rats who had been fed a diet deficient in vita

min A No other pathogenic factor common to all of the affected animals could be found These experimental results were confirmed by Fujimaki[10], who found that rats deprived of an adequate source of vitamin A for twelve weeks developed phosphate stones in the kidney and bladder and cholesterol stones in the bile ducts

McCarrison[11] showed that lack of vitamin A led to a keratinization of the epithelium of the urinary tract and suggested that the desquamated keratinized epithelium might serve as nuclei of stones All the stones in these experimental studies were composed of calcium magnesium phosphate The rapidity of stone formation was increased if the diet also was deficient in ascorbic acid, and if phosphates were fed Higgins[1] not only reported the production of phosphate stones in vitamin A deficient rats but in 2 of 4 dogs maintained on a deficient diet for 4 to 11 months and sand in the bladder of a third One of two Dalmatian puppies developed a uric acid and urate stone in the bladder in one and one half months Higgins also found urate deposits in the kidneys and ureters of chickens fed a vitamin A deficient diet

Although the association of urinary calculi with vitamin A deficient diets in rats and possibly of urate deposits in chickens and dogs seems established the relation of deficiency of this vitamin to the incidence of calculi in man is less clear Higgins[12] and Ezickson and Feldman[13] report a high incidence of vitamin A deficiency as measured by a biophotometric test of dark adaptation in patients with urinary calculi but do not report a control series Long and Pyrah[14] found 64 per cent of 25 patients had abnormal dark adaptation, which was present in only 25 per cent of normal controls Forty per cent of patients with seborrhea gave an abnormal reading on the biophotometer They concluded that deficiency was at most a contributing factor Jewett, Sloan and Strong[15] on the other hand could detect no difference in the dark adaptation of 20 patients with stone and 40 controls nor any difference in the concentration of vitamin A in the plasma Nor could they detect any of the metaplasia characteristic of vitamin A deficiency in the urinary tract or bronchi in 78 cases of nephrolithiasis examined postmortem Lassen[16] likewise could not confirm the decrease in liver function as measured by bromsulfalein test in cases of lithiasis as reported by Ezickson[17] Thus while the relation of the incidence of stone to the dietary habits and economic status of a people indicates the importance of dietary deficiency it is not clear that lack of vitamin A is of fundamental significance in the etiology of nephrolithiasis

Precalculus Lesion

Randall[18] has emphasized the importance of a precalculus lesion He reasoned that a stone must form by the gradual accretion of salts on a nidus and

that this nidus must remain fixed while the stone is growing otherwise it would be swept out as a small crystal in the urinary stream Randall studied the renal papillae in 609 pairs of kidneys at necropsy and found papillary lesions in 140 or 22 9 per cent and primary calculi in 24 or 4 1 per cent The precalculous lesion consisted of a deposit of calcareous material in the basement membrane of the collecting tubules and in the intertubular connective tissue Such intra papillary calcium plaques were of themselves innocent enough but when they occurred near the surface of the papillary wall they were prone to ulcerate the covering epithelium and when so denuded to serve as a nidus for precipitation of urinary salts and the formation of a stone Many instances were found of a small stone adherent to such a plaque which when it was removed showed a roughened area corresponding to a ragged papillary defect of similar size Randall postulates that the primary damage to the kidney leading to the development of the papillary lesion may be metabolic dietary or infectious and that in addition there must occur also a hypersecretion of certain urinary salts actually in supersaturation for a stone to form The frequent occurrence of such papillary lesions at autopsy has been confirmed by the work of Rosenow[19] Posey[20] and Vermooten[21]

Hyperparathyroidism

The work of Albright[22] and his associates has shown the frequency of calcium phosphate stones in cases of hyperparathyroidism whether this be due to tumor or simple hyperplasia of the glands The disturbance in metabolism in hyper parathyroidism is accompanied by an elevated serum calcium low phosphorus increased phosphatase and an increased urinary excretion of calcium Stones may occur in typical cases of osteitis fibrosa cystica or may be present without demonstrable bone lesions Occasionally the calcium phosphate is deposited in the collecting tubules or renal parenchyma leading to atrophy and insufficiency simulating Bright s disease These cases run a slow chronic course with a history of passing gravel for many years Barney and Mintz[23] found renal calculi in 15 of 65 cases of hyperparathyroidism reported in the literature and added 11 cases of renal stone in 18 cases of hyperparathyroidism observed at the Massachusetts General Hospital in which the diagnosis had been confirmed at operation The ages of these patients varied from 13 to 62 years Because a systemic disturbance is responsible for the calculous formation the stones tend to be bilateral multiple and recurrent Barney and Mintz believed that parathyroid disease appeared to be the causal factor in 10 per cent of cases of renal lithiasis This is considerably higher than the 0 2 per cent reported by Griffin Osterberg and Braasch[24] from the Mayo Clinic and that found by Higgins[12] at the Cleveland Clinic However in cases of hyperparathyroidism stones are present in about 70 per cent

Infection

The role played by infection in the production of urinary calculi is uncertain There is no doubt that infection is present in a high proportion of cases of lithiasis especially when there is some degree of obstruction But whether the infection is a cause or sequence of calculous formation is difficult to determine, for there are many cases of stone without infection and the common colon bacillus infection of the urinary tract is not frequently associated with stone Rosenow and Meisser[5] believed that focal infection elsewhere in the body was of importance in leading to the formation of calculi They reported the production of calculi or medullary lesions in 87 per cent of previously healthy dogs after inoculating their teeth with streptococci obtained from 9 patients with recurrent nephrolithiasis This work, however has not been confirmed so that there has been no general acceptance of this theory of etiology of renal calculi

Pyelonephritis is a frequent item in the history of patients with stone Bugbee[26] studied 23 such patients in whom initial roentgenograms revealed no calculi although stones subsequently developed in all The importance of infection with *Bacillus proteus* or other organisms, which have the power of splitting urea into ammonia and carbon dioxide with subsequent formation of relatively insoluble ammonium magnesium phosphate, has been emphasized by Hagar and Magath[7] and by Brown and Earlam[28] Chute and Suby[9] consider as urea splitters all cases of *B proteus*, *B pyocyaneus* and *H influenzae* infection and also those cases of staphylococcus colon bacillus and nonhemolytic streptococcus infection with alkaline urine They believe that the presence of urea splitting bacteria with the formation of an alkaline urine and consequent precipitation of calcium and magnesium phosphate, ammonium magnesium phosphate and calcium carbonate constitute the most common single cause of stone formation With aseptic stone the urine usually was acid

The importance of infection in recurrent nephrolithiasis seems on firmer ground Rovsing[30] found 71 per cent of all recurrences in kidneys primarily or secondarily infected with urea splitting organisms Infection however, usually is associated with some degree of obstruction to the outflow of urine and with the presence of an alkaline urine both of which are contributory factors to calculus formation It has been suggested that bacteria may form a nidus upon which insoluble salts are deposited by precipitation until a calculus is built up Hellstrom[31] found cocci in all layers of a calculus which he dissolved in hydrochloric acid and stained Joly[8] however points out that no bacteria can be found in the urine in the stones themselves or in the kidneys of patients suffering from primary calculi He concludes that infection is not necessary for stone formation and that at most it merely creates conditions which are peculiarly favorable for stone formation

Stasis

Closely related to the problem of infection is that of stasis There seems little doubt that when infection is present stasis favors the production of calculi or at least their more rapid growth Stasis may be due to congenital abnormalities such as horseshoe kidney or aberrent vessels to kinking or obstruction of the ureter or according to Rose[37] to a dyskinesia due to an abnormal capacity relationship between different portions of the pelvis and calices or the angle of junction of the calices Faulty drainage probably accounts in part at least for the frequency of the renal stones often bilateral in patients who have been kept flat in bed for long periods of time When an individual is kept on his back the highest point in the urinary tract is the ureteropelvic junction which imposes an abnormal obstacle to drainage from the upper tract so that if a deposition of crystals does take place they may be retained as nuclei of stones because the force of the urinary stream is not sufficient to wash them away[33, 34] Thus although stasis is undoubtedly a factor in some cases of renal stone it is not a primary cause for in many cases obstruction and stasis are absent In many patients immobilized because of osteomyelitis fracture or systemic disease a disturbance in calcium metabolism with an increased urinary excretion may also contribute to stone formation However a simple increase of calcium and phosphorus even with an alkaline urine does not lead to an increased incidence of stone formation The incidence of stones in patients who have had alkali treatment for peptic ulcer even over long periods of time is no higher than in control groups[35]

Sulfonamide Drugs

Since the introduction of the sulfonamide drugs many cases of urinary calculi due to their administration have been reported The acetyl derivatives of the sulfonamides in which form the compounds are chiefly excreted are relatively less soluble than the nonacetylated form and the free acids are less soluble than their sodium salts The concentration of these drugs in the urine may be 20 or 30 times the blood concentration as a result of reabsorption of water by the renal tubules The reabsorption of base lowers the pH of the urine from that of blood to 6 or 5 5 so that the soluble salts are converted into the relatively insoluble acids

When an adequate diuresis is not maintained the acetyl sulfonamides are precipitated in the collecting tubules which may become obstructed or the crystals may injure the walls of the pelvis and adhere to them Agglomeration into masses sufficiently large to block the ureter may produce anuria[36, 37] This mechanical anuria following sulfonamide therapy is distinct from the toxic nephrosis without obstruction which usually is seen in patients who have be

come sensitized by a previous course of drug Obstruction is more frequent after administration of sulfathiazole and sulfadiazine than after sulfapyridine and is rare after sulfonilamide itself

Composition of Renal Calculi

The composition of a renal stone is dependent in part upon the reaction of the urine at the time it is formed Phosphate and carbonate stones develop in an alkaline urine while oxalate uric acid and the rare cystine and xanthine calculi develop in an acid urine Every stone has a nucleus, which may be a minute crystal or a foreign body and is held together by a frame work whose chemical nature is unknown but which is presumed to be colloidal The stone formed around the nucleus may present a relatively homogeneous crystalline appearance or may show a laminated structure of alternate compact and more spongy layers in which the crystals are disposed irregularly with their interstices filled with colloid material A stone may consist entirely of oxalate phosphate or carbonate or may be a mixture of urates and oxalates or of phosphates and carbonates A stone which is predominately phosphate or carbonate, may contain some urate or oxalate Joly[8] points out that truly pure stones are rare and that any calculus which contains 90 to 95 per cent of any one salt may be regarded as a pure stone Calcium oxalate is the most common constituent of stones in America[35] Next in order of frequency are phosphate calculi ammonium, calcium or magnesium

Calcium oxalate stones are very hard and brown or gray in color They differ considerably in structure The surface may be smooth or covered with sharp glistening crystals or show a few long thorny processes These are the so called 'jack stone' calculi Another type the "mulberry' calculus is found usually in the bladder but is not uncommon in the kidney Its surface is closely covered with mammillary projections 3 to 4 mm in diameter except where it has been in close contact with the pelvic wall These are the roughest and most irregular type of calculus and tend to be retained until they require surgical removal

Phosphate calculi usually have a uric acid or oxalate nucleus The hard white stones of crystalline calcium phosphate are relatively rare The majority of phosphate calculi are mixtures of calcium and ammonio-magnesium phosphate with some calcium oxalate or carbonate These are relatively soft of a grayish color with a rough surface and an amorphous rather than crystalline structure They may fill most of the pelvis forming the so-called 'staghorn" calculus Phosphate stones are found in hyperparathyroidism with a persistently alkaline urine due to the presence of urea splitting organisms and in individuals whose diet contains an over abundance of calcium phosphate

Uric acid and urate stones are hard usually ellipsoidal and usually yellow

They may be crystalline or laminated Pure uric acid stones commonly are small rounded and smooth so that generally they are passed spontaneously Uric acid frequently forms the nucleus of phosphate or oxalate stones Uric acid and urate stones are commonly but by no means always associated with gout

Cystine calculi are formed in about 2 per cent of cases of cystinuria[39] This is an inborn error of metabolism in which there is a strong hereditary tendency The metabolic defect according to Brand and his collaborators[40], is concerned with the handling of methionine and cysteine Administration of either of these to a cystinuric increases the excretion of cystine while when cystine itself is fed, it is completely oxidized Cystine is one of the least soluble of the amino acids and is particularly insoluble at the hydrogen ion of normal urine Cystine calculi usually are crystalline with a smooth surface but rough and granular when mixed with phosphate In the pelvis they are often staghorn while in the bladder they are usually spherical Cystine stones usually occur in children are generally bilateral and tend to recur after removal

Xanthine calculi are encountered rarely and then usually in the bladder Like cystine stones they must be attributed to some error in the metabolism They are usually of a reddish brown color hard compact with an amorphous laminated appearance[41 4] Occasionally soft noncrystalloid stones , composed of inspissated pus fibrin or albuminous material are encountered in infected pyelonephrotic kidneys They vary in size from that of a pinhead to a centimeter are grayish white yellow or light brown in color cast no shadow on an x ray plate and are diagnosed rarely before operation Calculi have been found also which formed around foreign bodies left in the kidney by the surgeon or as a result of traumatic accident

The great majority of renal stones are formed first in a calyx especially the inferior calyx since this lies below the level of the upper portion of the ureter and consequently has the poorest drainage Joly[8] divides renal calculi into five clinical groups (1) small stones lying free in the renal pelvis or a calyx (2) stones impacted at the ureteropelvic junction (3) stones filling the renal pelvis (4) stones which have formed a mould of the pelvis and calyces staghorn calculi and (5) giant calculi which have destroyed the kidney so that the renal parenchyma is reduced to a mere shell surrounding a great mass of stone A small smooth stone washed from a calyx into the pelvis usually will enter the ureter without much difficulty while a rough or jagged concretion is more apt to become impacted at the ureteropelvic junction Here it gradually grows backward into the pelvis which adapts itself to the growing stone Stones do not grow to a large size when obstruction is present for this leads to impairment of renal function and dilution of the urine Stones composed predominantly of phosphates or of cystine tend to grow rapidly uric acid more slowly and oxalate stones still more slowly

Most bladder calculi probably originate in the kidney pass through the ureter and are retained in the bladder because of some abnormality causing obstruction to urinary evacuation as in enlarged prostate "cord bladder diverticulum or urethral stricture Primary bladder stones in the United States usually are formed about a foreign body an unabsorbed suture, fragment of catheter or some object introduced into the bladder by the patient In parts of South China and India however the incidence of bladder stone is much higher than renal calculus particularly among children This has been attributed to the deficient diets eaten in these countries The apparent decrease in the incidence of vesical calculi in this country and in England is referred to improvement in dietary habits of the population particularly those in the lower economic strata

PATHOLOGICAL CHANGES DUE TO CALCULUS

"A kidney which harbors a calculus always suffers from such an experience [43] Although even a large staghorn stone may remain in a kidney pelvis for years without producing symptoms sooner or later a calculous kidney becomes infected and infected calculosis is one of the most destructive lesions affecting the kidney Hence, even a small stone is a potential hazard to its possessor

Stones cause damage by local irritation obstruction compression and infection Infection may have preceded the formation of the calculus or have resulted from its presence The type and amount of damage done by a stone depends upon size shape and position A small concretion, which produces obstruction will do more damage than a larger one which permits free flow of urine around it A stone in the renal pelvis is a foreign body and causes inflammation of epithelial lining with desquamation of superficial cells thickening and roughening of the mucosa and a certain amount of interstitial fibrosis in the muscle layer Superficial ulceration and small hemorrhages in the wounded epithelium give rise to the red blood cells which are found in the urine When there is more or less constant obstruction to drainage and consequent increase in intrapelvic pressure some degree of hydronephrosis develops This usually is not marked The dilatation is intrarenal rather than pelvic possibly due to the thickening of the pelvic wall The presence of infection alters the pathological picture The growth of the stone and destruction of the kidney proceed more rapidly The pathological changes in the kidney are similar to those in noncalculous pyelonephritis Depending upon whether the stone obstructs only one calyx or the whole pelvis part or all of the kidney may be destroyed with the development of calculous pyelonephrosis When the whole kidney is involved it resembles a multilocular cyst with septa, once the walls of calyces separating pockets filled with mucus pus debris and stone

Stone in the bladder produces local mechanical irritation which varies with

the character of its surface and shape from a mild reddening and congestion when it is smooth and round to abrasion and hemorrhage when it is rough Infection quickly follows and all grades of inflammation and ulceration of the walls of the bladder result If the calculus obstructs the urethral opening intermittently it will cause or aggravate the changes due to back pressure hypertrophy and trabeculation of the bladder and dilatation of the ureters Bilateral pyelonephritis is a common complication of vesical calculus

Symptomatology

The characteristic symptoms of nephrolithiasis are spoken of as renal colic The pain of renal colic is due to an increase of pressure within the pelvis of the kidney It is caused most commonly by the passage of a small calculus down the ureter but identical symptoms are produced by the passage of any other body as a blood clot or mass of caseous material or by blocking of the upper end of the ureter by a stone in the pelvis which is too large to enter the ureter In the majority of cases the onset of pain is abrupt In some patients however who have had repeated attacks of colic there may be a premonitory feeling of weight or discomfort in the loin with some tenderness on pressure and a disinclination to move The actual onset of pain is sudden While this may be when the patient is at rest or even asleep it is usually provoked by exercise jolting a sudden jar or by work which involves bending the lumbar spine Thus attacks seem particularly frequent when a man of sedentary life takes a holiday The pain starts in the back in the angle between the last ribs and the erector spinae muscles spreads around to the front of the abdomen and then down along the course of the ureter In severe attacks the pain radiates to the scrotum and down the front of the thigh The testicle in these cases is retracted and tender and the skin of the scrotum thrown into folds and ridges by contraction of the dartos The pain is variously described as cutting tearing or burning but the most characteristic feature is the intensity The victim is unable to continue his work and lies writhing on floor or bed in a constant effort to find a position of relative comfort The pain although constantly present during an attack varies in intensity with acute paroxysms supervening from time to time Nausea and vomiting accompany the pain in half the attacks and may be incessant The pulse rate is accelerated blood pressure low and the skin pale and covered with a cold sweat Fever is unusual except when the kidney is infected Frequently there is moderate abdominal distention accompanied by constipation Occasionally there is rectal tenesmus with the passage of small watery stools There is increased frequency of micturition although the volume of urine is diminished The frequency of a desire to void increases as the stone passes down the ureter and is most marked when it lies in or just above the intramural

portion When a stone is in this position the patient strains every few minutes to pass a few drops of urine With relief of pain there is often polyuria An attack of renal colic may last only an hour or two or may persist for 48 hours The pain may cease abruptly or gradually When cessation is abrupt, the stone has passed from the ureter into the bladder, and usually is passed per urethra within 48 hours If however there is any obstruction in the prostate or urethra it may be retained in the bladder and develop as a vesical calculus When the stone is not passed into the bladder the pain gradually diminishes, usually following a dose of morphia or some other sedative and the patient falls asleep When he awakens the pain has gone but colic usually recurs again perhaps in a few hours perhaps not for several weeks These attacks recur until the stone is passed During the interval between attacks urine passes by the stone to reach the bladder

It is rarely possible to feel the kidney during an attack of renal colic due to the rigidity of the abdominal and lumbar muscles Tenderness in the loin is marked and increased by palpation of the abdomen as well as the back As a rule pressure applied in the costovertebral angle lateral to the erector spinae muscles gives rise to more pain than palpation elsewhere In spite of abdominal tenderness there is usually little or no rigidity of the rectus abdominalis Palpation along the course of the ureter is painful also and is most marked where it crosses the iliac arteries about 2 inches from the midline at the level of the umbilicus This is close to McBurney s point and may be misleading unless it is remembered that the point of maximum pain is much higher up and in the back

The urine always is scanty in an attack of renal colic and contains blood The blood may be intimately mixed with the urine giving it a smoky or distinctly red color or may be present as small clots in an otherwise clear specimen The amount of blood may be so small that it is only recognized on microscopic examination The presence of red cells usually serves to distinguish renal colic from the crisis of hydronephrosis In addition to blood, the urine in renal colic contains albumen crystal and desquamated epithelial cells from the ureter

Attacks of renal colic may be produced also by stones retained in the kidney pelvis when these are movable and obstruct the ureter intermittently As soon as the stone moves the pressure is released and pain ceases The duration of an attack is variable from a few minutes to several hours but usually is shorter than when the stone is engaged in the ureter Attacks are brought on by exercise and relieved by lying down If the calculus becomes fixed either in the renal pelvis or a calyx, these attacks of pain are apt to disappear and to be replaced by a dull fixed ache in the loin which again is increased by exercise and relieved by rest The pain may be described as radiating around the body but more commonly as boring through from back to front Definite tenderness usually can be elicited in the costovertebral angle on palpation There is little dis

turbance in micturition but microscopic blood usually is present in the urine and the amount is definitely increased by exercise The severity of the pain seems to be proportional to the roughness of the stone Thus it is greater with calcium oxalate stones which are covered with spines or sharp crystals than with the smooth uric acid or cystine calculi

When infection is present the symptoms of pyelonephritis may dominate the clinical picture A history of previous renal colic or passage of gravel can be obtained in about half the cases according to Joly[3] Attacks of pain are less frequent and severe and are apt to be accompanied by rigor and fever Pyuria is present The patient usually comes under observation because of symptoms of urinary tract infection and calculi are discovered during the routine study of this condition

Diagnosis

The diagnosis of renal colic usually is not difficult However if on the right side it must be differentiated from biliary colic and acute appendicitis In biliary colic the pain is most intense anteriorly tends to radiate to the epigastrium or right shoulder blade there is increased resistance of the right rectus muscle and the urine does not contain blood A history of dyspepsia is helpful and jaundice may be present Occasionally pressure in the costovertebral angle may give increased pain In such instances the patient should be examined when lying on his left side In this position the liver tends to fall toward the midline and pressure in the flank no longer increases the pain Renal disease is diagnosed more frequently as an affection of the gallbladder than the reverse

The differentiation between acute appendicitis and renal colic may be more difficult *If the kidney is prolapsed the differentiation may be extremely puzzling* for there may be a tender painful swelling in the right iliac fossa which resembles a chronic appendiceal abscess A clear urine fever and leucocytosis are characteristic of appendicitis but urinary symptoms frequency pain on micturition and occasionally hematuria may occur in appendicitis A correct diagno is may be impossible without the aid of roentgenograms or until after operation

The pain of calculus must be differentiated also from that due to disease of the lower thoracic or upper lumbar vertebrae With the latter the pain radiates around the body more horizontally is frequently accompanied by paresthesia or hyperesthesia and does not tend to radiate down to the testicle The spine is rigid and maximum tenderness is in the midline Cases of renal colic in which the pain is not definitely localized to the loin or along the course of the ureter may be mistaken for intestinal obstruction because of nausea vomiting constipation and abdominal distention The pain of a hydronephrotic distention comes on more gradually and is not subject to colicky exacerbations An enlarged kidney may be palpable and usually there is no blood in the urine Radiography

and catheterization of the ureters is necessary for a certain differentiation Renal tuberculosis is likely to be confused with lithiasis only in the early stages, later the predominance of bladder symptoms in tuberculosis usually indicate the correct diagnosis The early symptoms of renal tuberculosis may be an attack of pain accompanied by hematuria A new growth in the pelvis or medulla of the kidney may bleed and give rise to blood clots which retained in the pelvis or in passage down the ureter may give attacks of renal colic The presence of long thin ureteric clots is strongly suggestive of stone

Roentgenography is of the greatest value in the diagnosis of renal stone A plain x ray examination including kidneys ureters and bladder should be made in every case where the history suggests the possibility of stone If the patient is properly prepared renal stones can be demonstrated in a high percentage of cases because calcium oxalate and calcium phosphate, the principal constituents of renal stones cast very good shadows and there is usually enough of one of these salts in the relatively nonopaque urate, triple phosphate or cystine stones to form a detectable shadow However the absence of a shadow in a plain film cannot be accepted as proof that a calculus is not present in the kidney Frequently it is impossible to tell whether a small shadow along the course of the ureter is due to a stone or to a phlebolith A lateral plate may be helpful Usually a plain roentgenogram will show whether the stones are unilateral or bilateral and give some idea of their size shape and position While in some cases plain roentgenograms are adequate for accurate diagnosis in most instances further study by urography is necessary Excretory pyelograms will show whether the stone has formed in a horseshoe nonrotated ectopic or other congenitally anomalous kidneys and usually will suffice to show whether a suspicious shadow is in the ureter or outside it However if kidney function is impaired the concentration of dye may not be sufficient to produce a good shadow The most accurate diagnosis is obtained by cystoscopy catheterization of the ureter and retrograde pyelography This also permits collection of urine from each kidney and estimation of the amount of impairment which the stone has produced Higgins[14] has emphasized the importance of determining the reacton of the urine from the calculous kidney for in many cases this differs from that obtained from the sound kidney and bladder Since treatment designed to prevent recurrence will depend upon whether the stone has formed in an acid or alkaline medium this information is of great importance For the same reason the composition of every stone recovered should be determined by chemical analysis

Treatment

The treatment of renal colic requires large doses of analgesics and morphine is by far the most valuable Frequently 15 mgm (gr $\frac{1}{4}$) of morphine sulfate will

be inadequate to relieve the pain If the colic is severe it may be necessary to give 30 mgm (gr $\frac{1}{2}$) of morphine sulfate as the first dose and repeat 10 or 15 mgm doses as indicated *Atropine sulfate* 0 65 mgm (gr $\frac{1}{100}$) may relieve ureteral spasm Some success has been claimed by intravenous injection of calcium chloride or gluconate The management of nephrolithiasis consists of two parts removal of all stones present and the prevention of recurrent formation of additional calculi.

Every stone in the urinary tract is a hazard to its host, because of the dangers of obstruction and infection The choice of treatment will depend upon the size, number and position of the stones A small rounded calculus located in a calyx or in the pelvis if it is not large enough to block the ureter may be treated expectantly unless severe infection is present The patient should be given large quantities of water to promote diuresis in the hope that the calculus will enter the ureter and be passed If a stone shows a tendency to descend its course can be followed by serial roentgenograms and it may be temporized with for several months When this course is followed the patient must be impressed with the importance of remaining under regular observation A stone, which fails to make satisfactory progress down the ureter frequently may be dislodged by a ureteral catheter in the hands of an experienced urologist Medium sized and large stones should be removed by appropriate surgical procedures since serious damage to the kidney is sooner or later too likely to follow While the damage to the kidney at operation often appears much greater than suspected a surprising degree of recovery often follows removal of the stones and adequate drainage A kidney without evidence of marked sepsis or hydronephrosis there fore usually should be treated conservatively

A stone in a solitary kidney presents a serious and difficult problem Surgery usually is necessary and of course must be conservative In the presence of bi lateral calculi the least seriously damaged kidney usually is treated first The most urgent indication fortunately rare, for immediate surgical removal of a stone is when it has suddenly blocked one ureter and there is reflex inhibition of the other kidney with complete anuria

Dissolution of cystine calculi by keeping the urine alkaline over prolonged periods of time has been reported by Crowell[15] and by Albright[16] Occasionally a phosphate stone will disappear if the urine is kept strongly acid but as Albright points out if this is done by diet, while further precipitation may be prevented, the amount of calcium and phosphorus to be eliminated is increased so that the urine remains nearly saturated with these salts and dissolution of the stone is unlikely However dissolution of phosphatic calculi has been accomplished in a small series of cases by irrigation of the pelvis through a nephrostomy tube or ureteral catheter with solutions of citric acid and magnesium oxide[17, 18] The procedure requires several weeks to months of hospitalization No solution has yet been found which has any effect on urate or oxalate stones

The problem of preventing a recurrence of calculus formation requires careful study, minute attention to details and prolonged observation Attention must be directed to the possible presence of all the factors discussed under etiology Stasis and infection are common factors in recurrence In the treatment of infection, sulfathiazole or sulfadiazine is extremely useful When infection is due to organisms of the colon group an acid ash diet and sufficient acidifying agent, such as ammonium chloride to keep the pH of the urine between 5 0 and 5 2 is sufficient to eradicate the infection Lavage of the renal pelvis with anti septic solutions sometimes is used Remote foci of infection in teeth tonsils or sinuses should be eliminated if possible In most cases the patient should main tain a urinary output of 2 to 3 liters a day The more dilute the urine the less will be the precipitation of the urinary salts, and diuresis also helps to wash out pus and debris

Patients having calcium phosphate stones or when stones are bilateral and recurrent, should be studied for evidence of hyperparathyroidism by estimations of the levels of serum calcium and phosphorus and by roentgenography of the long bones for the characteristic osseous changes

Recent studies indicate that much can be accomplished in preventing recur rence of stones by attention to the reaction of the urine For calculi composed of phosphate or carbonate, which are more insoluble in alkaline solution, a high acid ash diet is indicated with sufficient ammonium chloride to maintain a urine pH of 5 0 to 5 2 while for calculi of urates or cystine an alkaline ash diet with additional alkaline salts if necessary to maintain a pH of 6 9 to 7 0 is pre scribed Foods with high purine content should be restricted to minimize the excretion of urates and uric acid There are however, certain hazards and diffi culties in the use of an acid regimen When kidney function is impaired the ability of the kidney to excrete an acid urine is diminished and acidosis with high plasma chlorides phosphates and sulfates and low carbon dioxide may result In the presence of infection with urea splitting bacteria the pH of the urine cannot be reduced and the increased amount of calcium and phosphate in an alkaline urine may lead to increased precipitation of these salts There is also an increased excretion of calcium when an acid ash diet is ingested, the effect being much more marked in some patients than in others The acid ash diet is most effective when it does not lead to any marked increase in calcium excretion These facts indicate the necessity for individual study of each patient By the use of such diets Higgins[1] reported a reduction in the number of recurrences from 16 4 to 4 9 per cent and Twinem[49] from over 20 per cent to 5 3 per cent Whenever any of the sulfonamide drugs are administered the possibility of pre cipitation in the collecting tubules and formation of stones in the calyces and pelvis must be kept in mind If precautions are taken to maintain an output of 1 000–1 500 c c daily of alkaline urine the risk is minimized[50]

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CHAPTER XIII

DISEASES OF THE ADRENALS

By ROBERT F. LOEB

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Introduction

Bartholomaeus Eustachius is credited with having first described the adrenal glands as specific organs in 1563. Furthermore, Eustachius described these suprarenal structures as glands at that time although their significance was in no way understood. Indeed it was not until 1855 that the importance of the adrenal glands in body economy became apparent. At that time Thomas Addison demonstrated in his classic treatise entitled, "On the Constitutional and Local Effects of the Suprarenal Capsules," that these organs were essential for life and that their complete destruction in man resulted in the fatal disease which today bears his name. In the year following the publication of Addison's studies Brown Sequard demonstrated in animals that total ablation of the adrenal glands resulted in death and thus emphasized the importance of Addison's clinical observations. Despite these dramatic and provocative observations the nature of the functions of the suprarenal capsules did not begin to be clarified for another forty years, that is until Oliver and Schaefer in 1894 first demonstrated the striking pressor effect of extracts of the adrenal medulla. This physiological activity once demonstrated stimulated the study of adrenal medullary function which has gone on unabated since that time. These researches have not only extended our knowledge concerning the function of the adrenal medulla but have demonstrated the great importance of its active principle in the field of therapy.

For many years the most intensive study of adrenal function was limited to that of epinephrine despite the fact that it had been shown early that this product of the adrenal medulla would not maintain life in a totally adrenalectomized animal. These observations clearly indicated that the substance or substances essential for life maintenance were elaborated by the cortical portion of the gland and not by the medulla. Yet it is only since 1928 that concerted effort has been made to unravel the mysteries surrounding the nature of these vital adrenal cortical functions. In this short time however great progress has been made and the integrated observations of chemists, physiologists and clinicians offer a most gratifying chapter in the history of the development of medical science.

Anatomy

Gross Anatomy

The adrenal glands are two small yellowish brown flattened structures which lie on each side of the spine retroperitoneally and in close proximity to the upper

pole of each kidney The two glands which have an average weight of 3 5 to 5 0 grams *each usually are of different shape the right being triangular and the* left more crescentic They are about 45 mm in length 30 mm in width and vary from 2 to 10 mm in thickness The size varies considerably with various physiological and pathological processes Thus in patients dying of infections the glands often are larger than normal as are the glands of animals subjected to severe exercise cold sustained anoxia or to any other state associated with an increase in protein catabolism according to the views of Long The increase in gland size usually is associated with histochemical evidence of increases in adrenal cortical activity e g a decrease in the cholesterol content

The adrenal glands in man consist of parts termed the cortex or interrenal tissue and the medulla or chromaffine or phaeochrome tissue The cortical tissue in man is rubbery in consistence and comprises about 90 per cent of the gland by weight The medulla on cut section is soft grayish in color and upon contact with chromates develops typical dark brownish pigment from which it derives the name of chromaffine tissue The medullary tissue is stained blue with iron salts and black with salts of osmic acid

In man the medullary tissue is surrounded completely by cortical tissue but in the lower vertebrates the two types of tissue constitute distinct and separate structures There appears to be a correlation between this evolution of the higher vertebrates and the intimacy of association between the interrenal and chromaffine tissues The union of cortical and medullary tissue is encountered first in amphibia Whether the close association as it exists in man has physiological implications is not known but studies by Vogt indicate that epinephrine causes immediate and long standing stimulation of cortical activity in the eviscerated dog or cat

The suprarenal capsules have an extraordinarily rich blood supply inasmuch as a branch from the aorta one from the inferior phrenic and one from the renal artery reach the cortical portion of each gland where they form rich plexuses The blood courses between the columns of cells of the cortex and then passes into the sinusoids and capillary network of the medulla The blood then enters the central vein which on the right enters the vena cava and on the left the renal vein Whether the mixing of capillary blood from the cortex with that of the medulla has any chemical or physiological significance has not been established A small amount of blood from the adrenal cortex appears to enter the portal circulation directly through minute veins communicating with branches of the splenic and pancreatic veins The blood flow through the adrenal glands is rapid and has been estimated as 6 to 7 c c per gram of tissue per minute

The lymphatics of the adrenal glands run between the columns of cells in the cortex as do the capillaries and ultimately form a plexus about the central vein in the medulla and drain into thoracic lymph nodes The nerve supply of the

Introduction

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Accessory Adrenal Tissue

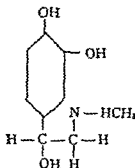
Groups of cells either of cortical or of medullary tissue are found frequently beyond the confines of the adrenal glands Thus chromaffine cells appear in the ganglia of the sympathetic chain They also appear in the carotid body and in the Zuckerkandl body at the bifurcation of the abdominal aorta These small islets of cells may be found elsewhere but usually they are in the retroperitoneal tissue near the adrenal glands

In certain species of animals notably the mouse rat and rabbit accessory adrenal glands containing sufficient numbers of cortical cells to maintain life are frequent This is important to bear in mind inasmuch as their possible presence often makes the interpretation of ablation experiments in these animals hazardous

Physiology

The Adrenal Medulla

The active principle of the extract of the adrenal gland which had been observed in 1894 by Oliver and Schaefer to have pressor effects was studied extensively by Abel who published in the Bulletin of the Johns Hopkins Hospital the following papers in 1897 to 190 On blood pressure raising constituents of the suprarenal capsule (with Crawford) page 151 1897 Further observations on the chemical nature of the active principle of the suprarenal capsule page 215 1898 On the behavior of epinephrin to Fehling s solution and other characteristics of this substance page 1 Nov 1901 and On a simple method of preparing epinephrin and its compounds page 9 Feb 1902 These studies extended greatly our knowledge of the action of epinephrine and described its isolation as a benzoyl derivative During 1901 Aldrich a former associate of Abel and Takamine reported separately the preparation of the active principle in crystalline form This Takamine patented under the name adrenalin In 1904 and 1905 epinephrine was synthesized independently by Stolz and by Dakin who ascribed the following structural formula to this secondary alcohol



adrenal glands is derived primarily from the splanchnics, and the fibers, according to Elliott, like those to the sympathetic ganglia are medullated preganglionic and of the cholinergic type There is a central control for epinephrine discharge, probably in the medullary vasomotor centers and in the hypothalamus The cells of the adrenal medulla probably are modified ganglion cells

Histology

Upon microscopic examination the adrenal cortex in man is divided from without inward into three zones These are known as the zona glomerulosa the zona fasciculata and the zona reticularis In the fetus a fourth zone designated by Grollman as the androgenic zone constitutes the major portion of the gland This layer normally disappears during the first year of life The glomerular zone is comprised of clumps of small round cells surrounded by fine strands of connective tissue and capillaries The fascicular layer which forms the greater part of the adult cortex is composed of columns of cells containing granules and droplets of cholesterol esters The cells of the reticular zone are large and rounded and filled with granules According to Zwemer the cells of the cortex move toward the center to replace the innermost cells which are constantly dying' Zwemer has shown that in the rat the cells of the cortex are completely replaced by new cells approximately every 30 days For this reason various degrees of degenerative changes appear in the reticular zone particularly in response to infectious or toxic processes or other forms of stress At the same time mitotic figures are numerous in the glomerular and outer fascicular layers

The adrenal medulla is composed of networks of large granular polygonal cells without any particularly regular arrangement and having the characteristic affinity for chromium salts Between these cells are found the sinusoids sympathetic nerve fibers and ganglion cells The medullary portion grows rapidly after birth at which time epinephrine can first be demonstrated in the glands

Embryology

The adrenal cortical tissue is of mesodermal origin It arises from the ventral portion of the epithelium of the cœlom and its development starts at the beginning of the fourth week The adrenal medulla with the rest of the chromaffine system on the other hand is of ectodermal origin and arises in conjunction with the sympathetic nerve cells from the neural crest The sympathetic nervous system and the chromaffine system not only arise together but the cells of the medulla and sympathetic ganglia show similar pharmacodynamic responses to physostigmine atropine and nicotine According to Grollman the differentiation of the chromaffine cells begins in the 18 mm embryo but as has been stated, the cells do not elaborate epinephrine until after birth

and with different dosage but averages 10 to 50 mm Hg with doses of 0 3 to 1 0 mgm when injected subcutaneously The diastolic pressure usually falls under these circumstances In the heart epinephrine increases contractility and irritability to a point at which ventricular premature contractions and even ventricular fibrillation may be induced with intravenous injection The increased irritability of the myocardium is reflected by the fact that adrenaline excites the idioventricular pacemaker in complete heart block It also shortens auriculoventricular conduction time when it is prolonged as a result of vagal or other action The hormone also causes an increase in heart rate According to Blumgart cardiac output increases on the average 75 per cent and may be increased as much as 140 per cent after the usual clinical dose The effects of epinephrine injected subcutaneously in man increase for about 30 minutes and then gradually subside Intravenous injection gives rise to more prompt and intense responses and may be fraught with dangerous consequences

Effect of Epinephrine upon Respiration — The most striking effect of epinephrine upon the *lungs* is to relax the smooth muscle of the bronchi and this is seen most dramatically in the alleviation of an attack of bronchial asthma As stated there is little effect of the hormone upon pulmonary blood vessels and its effect upon bronchial secretion is not clearly established Immediately after the administration of epinephrine there may be momentary apnea believed to result from carotid sinus stimulation This is particularly marked when the hormone is given intravenously which as stated is a dangerous procedure

Effects of Epinephrine upon Other Organs — Epinephrine causes contraction of the *splenic capsule* In man probably this is not of great importance as the spleen contains normally a relatively small amount of blood In the dog on the other hand contraction of the spleen in response to hemorrhage exercise and other conditions associated with the liberation of epinephrine may serve a useful purpose by increasing significantly the circulating red blood cells

In the *digestive tract* adrenaline has the following effect according to Goodman and Gilman The motility and tone of the *stomach* and *intestine* are decreased the sphincters contract as a rule and possibly secretion is inhibited Epinephrine induces contraction of the *gall bladder*

In the *skin* epinephrine calls forth a pilomotor response and inhibits sweating It inhibits *salivary secretion* In pregnancy epinephrine stimulates *uterine contraction* and has doubtful inhibitory effect on the organ in the absence of pregnancy

In addition to the effects described epinephrine frequently induces apprehension weakness dizziness tremor and precordial distress even when administered subcutaneously in the usual clinical dosage of 0 3 to 1 0 mgm It also shortens the *coagulation time of the blood*

Effects of Epinephrine on Metabolism — The outstanding effects of epinephrine upon metabolism are to increase the blood sugar and lactic acid and to

Epinephrine the first hormone to be isolated in crystalline form and synthesized possesses levo dextro and racemic forms of which the natural levorotatory compound is approximately 15 times as active as is the dextro form Epinephrine is unstable in alkaline solution and is more stable in blood than in salt solution It is stabilized by cevitamic acid and glutathione which is of interest owing to the fact that these reducing substances occur in the adrenal glands in high concentrations It is believed that the precursor of epinephrine in the body is either phenylalanine or tyrosine

Since epinephrine constitutes the only known physiologically active compound elaborated by the adrenal medulla consideration of the actions of epinephrine implies a consideration of the functions of the adrenal medulla

It may be said at the outset that adrenaline acts upon structures innervated by sympathetic nerves and its action is similar in those structures to effects of sympathetic nervous system stimulation i e it has sympathomimetic activity and it acts upon the myoneural junctions in smooth muscle Epinephrine is liberated from the adrenal glands by stimulation of the hypothalamus or of the sympathetic fibers of the cholinergic type to the glands It is also liberated in response to the emotions of fear and rage, as emphasized by Cannon, by increased muscular activity excessive heat or cold, asphyxia, hemorrhage, hypoglycemia and the action of certain drugs including acetylcholine histamine and probably certain anesthetics

By virtue of the fact that epinephrine shows sympathomimetic activity it might be anticipated that the manifestations of its action would be manifold Thus it has been shown to have striking effects upon the circulatory system upon smooth muscle carbohydrate metabolism total metabolism and other functions A consideration of the effects of epinephrine is essential for an understanding of adrenal medullary activity

Effects of Epinephrine upon the Circulation — The chief action of epinephrine is exerted upon the arterioles although epinephrine also acts to a varying extent upon larger arteries capillaries and veins Curiously enough the action may be of an opposite nature on different vessels as is true of sympathetic stimulation For example the most widespread action is that of arteriolar constriction, which occurs in the vessels of the skin mucous membranes and cerebrum i e vessels the smooth muscle of which is rich in adrenergic nerve fibers On the other hand, epinephrine dilates the coronary arteries and the arterioles of striated muscle during contraction and has but little effect upon the pulmonary arterioles This type of response on the part of the heart lungs and striated muscle is perhaps of teleological interest as suggested by Cannon It permits increased blood flow in those structures where this is of importance to the organism under the emotional stress of fear and rage The constriction of peripheral vessels results in an increase in systolic arterial pressure which varies greatly in different individuals

in the past 15 years that the mechanisms involved in the development of adrenal insufficiency have in a measure been clarified Unlike the medulla which as far as is known elaborates but a single hormone with various actions the cortex is the source of a group of active chemical substances These substances are steroids which despite close chemical resemblance are strikingly different in physiological activity Twenty-eight steroids have been isolated from the adrenal cortex The structural formulas of six possessing physiological activity are shown in Fig 1

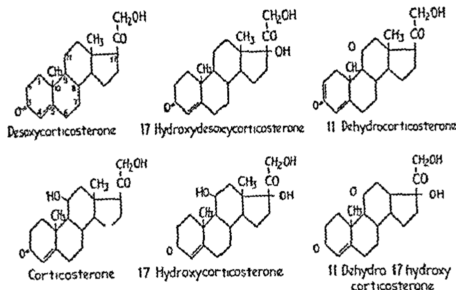


Fig 1 Structural formulæ of physiologically active steroids isolated from the adrenal cortex

The isolation of these hormones has been accomplished chiefly by Kendall and Wintersteiner and Pfiffner in this country and by Reichstein in Switzerland Reichstein in 1937 synthesized desoxycorticosterone which has become most useful in the treatment of hypoadrenalism in man In addition to steroids with classical adrenal activity progesterone androgenic substances including adrenosterone androstane 3 (β) etc and estrone have been isolated from the adrenal cortex Whether they are chemical artifacts or whether they occur there naturally is not known

It has been shown by Kendall that the amorphous steroid mass which remains after the removal of the known hormones possesses a high degree of physiological activity This suggests that other steroids of physiological significance remain to be isolated Lowenstein reports the isolation of an ascorbic acid-steroid com

raise the basal metabolic rate Thus in a group of normal human subjects the writer found that the blood sugar rose on the average 79 per cent in one hour and the blood lactic acid 190 per cent in the same time following the subcutaneous injection of 1 ml of a 1 1 000 solution of epinephrine The concentrations of glucose and lactic acid usually return to normal in two hours If the elevation of blood sugar in response to epinephrine exceeds the renal threshold, naturally glycosuria is observed The basal metabolic rate rises approximately 20 to 40 per cent following the subcutaneous injection of 0 5 mgm of epinephrine

The effect of epinephrine upon the blood sugar results from the fact that it increases the rate of glycogenolysis in the liver The increase in lactic acid results from an increased breakdown of muscle glycogen Part of the lactic acid is oxidized, and the remainder is carried to the liver and reconverted into glycogen thus preventing the depletion of glycogen stores When the glycogen content of the liver is low epinephrine causes a smaller rise in blood sugar than when glycogen storage is great

The calorigenic action of epinephrine is not due solely to an increase in the degradation of glucose In a fasting animal according to Cori the extra calories are derived exclusively from oxidation of fat, in the post absorptive animal in which a mixture of carbohydrate and fat is being oxidized, epinephrine also increases the metabolism without much change in proportion of the foodstuffs burned'

Epinephrine serves an important function in the regulation of the blood sugar level It is generally believed that hypoglycemia causes the discharge of epinephrine from the adrenal medulla and that this in turn causes glycogenolysis in the liver with an elevation of the blood sugar Liberation of epinephrine also increases the liberation of lactic acid from muscle glycogen This lactic acid then becomes a source for the restoration of the hepatic glycogen stores In the adrenalectomized animal and in patients with disease of the adrenal glands spontaneous and prolonged hypoglycemia as well as striking sensitivity to small doses of insulin may be at least in part, explained by the loss of the usual liberation of epinephrine

Despite the great array of physiological responses to stimulation of the adrenal medulla, i e to epinephrine, it must be reemphasized that this portion of the adrenal glands is not essential for life Indeed it now seems unlikely that the adrenal medulla is of great importance to the resting animal This view is borne out by the fact that animals which have had both adrenal glands removed, survive indefinitely and in good health when treated with a potent extract of the adrenal cortex in the absence of epinephrine

The Adrenal Cortex

The destruction of the adrenal cortex gives rise to a series of physiological disturbances collectively termed adrenal insufficiency or hypoadrenalism It is only

of the normal functional activity of the cells of the renal tubules It is also generally believed now that the decrease in serum sodium the hemo-concentration and the increase in serum potassium result from failure of the normal reabsorption of sodium and water by the renal tubule cells as well as from an increased reabsorption of potassium These disturbances probably result from the lack of a steroid of the type of desoxycorticosterone which normally exerts its influence upon the renal epithelium

The decrease in sodium in adrenal insufficiency is not limited to the blood stream The amount excreted in the urine is far in excess of that lost from the blood plasma and it may be concluded that this excess is lost from the interstitial fluid Whereas water is lost from the blood stream and interstitial tissue in adrenal insufficiency Darrow and also Muntwyler have shown that part of this fluid is shifted to the intracellular compartment and part is excreted by the kidneys This shift to the tissues takes place to maintain osmotic equilibrium in response to the abnormally large amount of sodium lost through renal excretion

It was shown by the writer that the clinical picture of acute adrenal insufficiency with the chemical disturbances described could be induced in the Addisonian patient by the simple procedure of restricting the amount of sodium in the diet to about 1 5 grams daily It was shown also that many patients could be restored to relatively good health with complete correction of the disturbances of electrolyte metabolism merely by increasing the sodium intake of the diet It was shown subsequently by Harrop and also by Allers that the completely adrenalectomized dog may be maintained in moderately good health indefinitely provided the intake of the sodium ion is maintained at an adequate level Thus no cortical hormone of any type is necessary for the mere survival of the animal It is for this reason that the *adrenal cortical function of life maintenance at least in certain species has become identified with the control of the metabolism of certain electrolytes and water*

Zwemer has shown that adrenalectomized animals have a particular susceptibility to the ingestion or injection of the potassium ion This observation finds its explanation in the fact that the excretion of this ion as already mentioned is diminished in the presence of adrenal insufficiency Harrison and Darrow ascribe this disturbance to an increase in the reabsorption of potassium by the renal tubules in the absence of certain hormones but it is of interest that the disturbance in potassium metabolism is also corrected by the administration of an adequate sodium intake

Effect of Adrenal Steroids upon Electrolyte and Water Metabolism — Of all the steroids isolated from the adrenal cortex one in particular *desoxycorticosterone* has a striking and particular effect upon electrolyte and water metabolism Certain of these effects are illustrated in Fig 2 As a matter of fact the effect of desoxycorticosterone esters is qualitatively identical with that of sodium adminis-

pound which is present in comparatively large amounts in the adrenal cortex and which has been crystallized This substance is about six times as active as is desoxycorticosterone for life maintenance and almost as active as 11 dehydro-17 hydroxycorticosterone in its effect on the work capacity of the rat It seems possible therefore that the active steroids found by the usual methods of isolation may constitute either building blocks or degradation products of a parent compound

Vogt has assayed the blood from the suprarenal veins of dogs for adrenal cortical activity by its effect on the survival time of young adrenalectomized rats subjected to cold (Selye test) On the basis of these studies it is estimated that a 10 kg dog under the conditions of anesthesia and operation employed, secretes daily about 230 ml of a commercial extract or the amount of active material obtained from 17 300 gm of gland tissue

Functions of the Adrenal Cortex — Two distinct groups of functions of the adrenal cortex have been firmly established These are (1) effects upon electrolyte and water metabolism which are closely correlated with life maintenance and (2) effects upon protein and carbohydrate metabolism This second function may be termed an emergency function and is apparently not necessary for the organism under the minimal requirements of existence On the other hand under all forms of stress to which the organism may be subjected Long believes that protein catabolism is increased Under these circumstances this emergency function of the cortex is called upon and is essential for the survival of the organism

Life Maintenance Function of the Adrenal Cortex — Total ablation of the adrenal glands in animals or their destruction by disease in man is associated with the progressive development of weakness prostration nausea, vomiting arterial hypotension dehydration oliguria and shock which terminate fatally The similarity of this chain of events to that observed in patients or animals in which loss of inorganic base has been known to occur is apparent In 1932 it was shown by the writer that the development of acute adrenal insufficiency in man is accompanied by a number of profound *disturbances in electrolyte and water metabolism* In the presence of acute adrenal insufficiency there is a striking decrease in the concentration of sodium in the blood serum with a corresponding decrease in chloride bicarbonate or both This is accompanied often by an increase in serum potassium There is loss of water from the serum attended by an increase in hematocrit and some increase in serum protein concentration With the advance of adrenal insufficiency there is a progressive decrease in circulating plasma volume which in time results in a decrease in urinary output and a decrease in renal function as manifested by nitrogen retention and retention of inorganic sulphate and phosphate There is fixation of specific gravity of the urine and a decrease in ammonia formation which appear to result from failure

sodium concentration in the blood stream and a decrease in potassium concentration In normal dogs prolonged administration of desoxycorticosterone also causes a syndrome of muscle weakness with replacement of as much as 30 per cent of the intramuscular potassium by sodium There also develops a striking diabetes insipidus like syndrome Desoxycorticosterone also causes an *increase in blood pressure* to abnormally high levels particularly when hypertension has been present before the development of adrenal insufficiency Perera and associates have noted also the gradual development of arterial hypertension in 8 of 24 patients with Addison s disease treated with desoxycorticosterone acetate in whom there was no evidence of previous hypertensive disease Furthermore Selye has demonstrated the development of arterial and renal lesions in normal animals treated with massive doses of desoxycorticosterone and sodium chloride

Corticosterone has definitely less effect than has desoxycorticosterone upon electrolyte metabolism Nevertheless it too causes retention of sodium and augments the excretion of potassium These effects have been demonstrated in man as well as in the adrenalectomized animal Another steroid of the adrenal cortex *11-dehydro 17 hydroxycorticosterone* known as *compound E of Kendall* is reported by Thorn to have no sodium sparing action Indeed Thorn states that it actually increases the excretion of sodium slightly This is in harmony with the observations of Ingle which demonstrate that corticosterone and compound E are much less effective as life maintaining hormones than is desoxycorticosterone On the other hand these substances possess other significant physiological activities which are not shared by desoxycorticosterone It is thus apparent that there is definite correlation between the chemical structure of the various steroids of the adrenal cortex and their physiological activities

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EFFECT OF TEN DAYS TREATMENT WITH DESOXYCORTICOSTERONE PROPIONATE

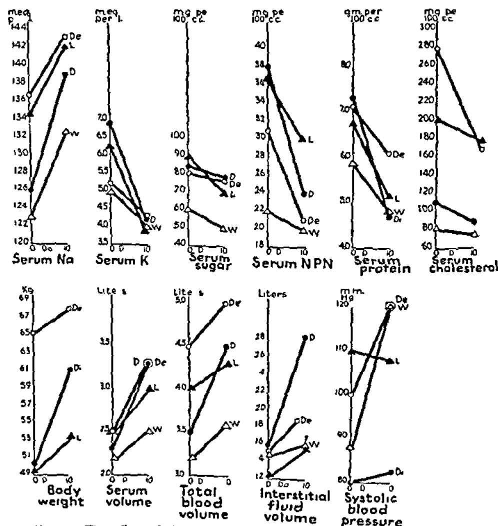


FIG 2 The effect of desoxycorticosterone esters upon certain physiological disturbances present in hypoadrenalism

desoxycorticosterone in the presence of adrenal insufficiency may cause edema and even massive anasarca when administered in excessive dosage Administered in excessive amounts, desoxycorticosterone induces an elevation of the

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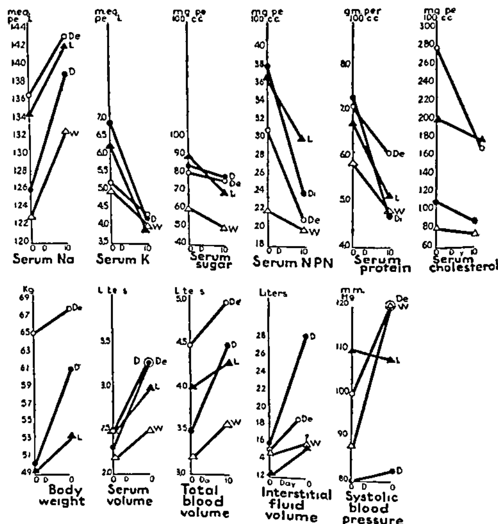


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Miscellaneous Adrenal Cortical Functions — A number of disturbances the natures of which have not been wholly clarified are encountered in patients with Addison's disease or in adrenalectomized animals It is possible that some of these are secondary to the decrease in blood flow resulting from loss of salt and water from the blood stream Others may follow the disturbances described in carbohydrate and protein metabolism For example the *basal metabolic rate* in adrenal insufficiency usually is lowered moderately Bromsulphalein tests indicate that mild degrees of *hepatic insufficiency* usually are present in hypoadrenalism, retention of from 5 to 15 per cent at one half hour being the rule in patients with Addison's disease *The blood calcium* for reasons unknown is elevated occasionally in adrenal insufficiency Thus the writer has observed serum calcium levels in excess of 12 mgm per cent in 3 patients The *absorption of glucose and fat* from the intestine is seriously impaired in severe adrenal insufficiency This was attributed by Verzar to a failure of phosphorylation of these substances in the intestine in the absence of the adrenal glands Recent studies however suggest that absorption of glucose and fat is normal if the circulating blood volume is restored with saline solution

Pigmentation is a common feature in patients suffering from chronic hypoadrenalism and has also been observed to develop in adrenalectomized rats Spoor and Ralli have shown an increase of phenolic compounds the precursors of melanin and of melanin itself in the skin of the adrenalectomized rat The importance of cortical rather than medullary insufficiency as the basis for pigmentation is indicated by two patients observed by the writer at autopsy These patients who had typical Addison's disease were deeply pigmented and were found to have virtually complete atrophy of all cortical tissue whereas the medullary portions of the glands appeared essentially normal It seems doubtful that desoxycorticosterone influences the pigmentation in hypoadrenalism Patients under treatment with salt or desoxycorticosterone esters often appear lighter with rehydration and stretching of the skin and in certain instances pigmentation decreases strikingly over the course of years This is true of patients treated with salt alone as well as of patients treated with desoxycorticosterone This may result from spontaneous regeneration of adrenal cortical tissue The effect of the other adrenal cortical steroids upon pigmentation is not known

tinued administration or the injection of adrenotrophic hormone causes hyper glycemia and heavy glycosuria in the normal animal just as had been shown earlier to be the case in diabetic or phlorhizinized animals Thus these hormones exhibit an anti insulin action The absence of these hormones, which are obviously of great importance in gluconeogenesis, explains the appearance of hypoglycemia and the low concentrations of glycogen in the liver of adrenalec tomized animals and also the extraordinary sensitivity to insulin in adrenal cortical insufficiency

Adrenalectomized animals maintained either with sodium chloride or with desoxycorticosterone have a greatly reduced capacity to perform muscular work as shown by Ingle If exercise is prolonged hypoglycemia develops, and in time animals die despite the repeated injection of glucose On the other hand, Ingle has shown that potent cortical extracts or the steroids known to influence carbohydrate and protein metabolism when given in conjunction with salt or desoxycor ticosterone life maintaining hormone greatly augment the capacity of the organ ism for muscular work

Selye has emphasized the importance of the adrenal cortex in relation to what he has termed the alarm reaction' Long and others have commented upon the fact that adrenalectomized animals are vulnerable to many forms of stress other than that of physical exercise In the intact animal these forms of stress which include trauma of various types cold anoxia hemorrhage burns acute infection and others regularly stimulate enlargement of the adrenal glands in the course of a few hours These forms of stress also bring about prompt depletion of the as corbic acid content of the adrenal glands perhaps indicating rapid secretion of the mother compound described by Lowenstein There is also a decrease in the cholesterol content of the glands demonstrable both histologically and chemically under these circumstances in 3 to 6 hours Weil and Browne, Venning and Browne and others have shown that the types of stress mentioned are asso ciated with an increase in the urinary excretion of material which prolongs the survival of adrenalectomized rats exposed to cold Furthermore Venning and Browne have shown that this corticoid material increases the storage of glyco gen in the liver of the fasted adrenalectomized rat This augmented excretion usually reaches a peak in severe injury in about 9 days Supporting the view that this "corticoid material is of adrenal origin is the fact that Venning and Browne have found that 7 to 12 per cent of adrenal cortical extract injected intravenously appears in the urine and possesses the same biological characteristics as the products of stress They have determined also that the increase in corticoid' excretion in stress may be 10-fold and equivalent to 100 to 200 micrograms of corticosterone daily Long advances the hypothesis that the forms of stress associated with increased excretion of corticoid material are those demanding an increase in protein catabolism In the presence of these ' emergency states' it

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Function of the Adrenal Cortex in Relation to Other Glands — The function of the adrenal cortex is under the influence of the anterior lobe of the pituitary gland In the absence of the latter structure atrophy of the adrenal cortex takes place After hypophysectomy atrophy of the adrenal cortex can be prevented by adequate administration of adrenotrophic hormone In the absence of the adrenal glands atrophy of the thyroid gland occurs fairly frequently The presence of hyperthyroidism intensifies the manifestations of adrenal insufficiency and raises the requirements for desoxycorticosterone Adrenal insufficiency on the other hand is ameliorated by hypothyroidism White and Dougherty have shown that both adrenotrophic pituitary hormone and adrenal cortical extract cause disintegration of lymphocytes in the thymus and lymph nodes This degeneration of lymphocytes is associated in less than 6 hours with an increase in the circulating gamma globulin As might be anticipated the increase in gamma globulin which is believed to be liberated from the lymphocytes results in an increase in circulating antibodies Desoxycorticosterone produces none of the effect noted

The importance of the effect of adrenal cortical stimulation in problems of immunity is not established Atrophy of the adrenal glands or their ablation is associated also with a decrease in the basophilic cells in the hypophysis Destruction of the adrenal glands in man is associated with a decrease in the ketosteroid content of the urine in the adult male and its disappearance in the urine of the female This suggests strongly that at least a portion of the urinary ketosteroid normally is elaborated by the adrenal cortex Disease or destruction of the adrenal cortex is not, however, associated with any significant disturbance of sexual function in either the male or female Adrenal insufficiency is ameliorated in pregnancy probably by virtue of increased hypophyseal activity, and also because the large amounts of progesterone have a mild effect upon salt and water metabolism analogous to that of desoxycorticosterone

Hyperactivity of the adrenal cortex produces striking effects in the organism This will be discussed in a subsequent section

Diseases of the Adrenal Glands

Diseases of the adrenal glands can be divided into two groups those associated with a decrease in their physiological activity hypoadrenalism and those in which their functional activity is increased or perverted, hyperadrenalism The diseases in which functional activity is decreased all involve the cortical portion of the glands as well as the medulla There are no known diseases resulting from insufficiency of the adrenal medulla alone Diseases of the adrenal cortex or medulla associated with over function or perversion of function frequently result from neoplasms or hyperplasia of these structures

Hypoadrenalism Addison's Disease

Incidence and Etiology

The syndrome termed Addison's disease which is the usual form in which hypoadrenalism (adrenal cortical insufficiency) occurs in man may develop at any age More than 50 per cent of the cases appear however between the ages of 30 and 50 years In the writer's series the youngest patient was 10 years and the oldest 68 years The disease is more prevalent in males than females about three fifths of the cases being seen in the former sex

Tuberculosis is responsible for the destruction of the adrenal glands in 65 to 80 per cent of patients with hypoadrenalism Tuberculous infection of the adrenal glands contrary to expectation is associated only occasionally with active pulmonary tuberculosis More frequently it is found in association with tuberculosis of the genitourinary tract and of the bones and joints It is of interest that despite the high frequency of tuberculosis in the colored race Addison's disease due to tuberculosis is relatively rare in this group Thus in a series of about 100 patients followed by the writer only 4 occurred in negroes In 3 of these cases the diagnosis was established at autopsy

In the patients who develop Addison's disease from non tuberculous causes hypoadrenalism usually results from atrophy of the adrenal glands The reason for this atrophy in individuals without obvious destruction of the anterior lobe of the pituitary gland Simmonds disease has not been established In two of the writer's cases atrophy of the adrenal glands was associated with florid tuberculosis elsewhere in the body In a third patient complete atrophy of one gland and tuberculosis of the other gland were found at autopsy

Very occasionally hypoadrenalism results from the destruction of the adrenal glands from a variety of causes including metastatic neoplasms syphilis infarction hemorrhage or amyloid disease

Pathological Anatomy

In cases of Addison's disease resulting from tuberculosis the glands often are replaced by caseating masses of tuberculous granulation tissue which frequently are 2 or 3 times the size of the normal structure In other cases where healing has taken place and deposits of calcium salts and fibrous tissue are interspersed with more recent tuberculous infiltration both the cortex and medulla are destroyed by the infection

In patients dying from atrophy of the adrenal glands both the cortex and medulla are as a rule involved The degree of atrophy often is marked and only with the aid of serial sections may it be possible to demonstrate any remaining

cells of the cortex or medulla On the other hand, in two of the writer's patients there has been virtually complete disappearance of cortical tissue with little or no involvement of the medulla

There are pathological changes in other structures which are frequently encountered in patients dying from hypoadrenalism Thus, a decrease in basophilic cells in the hypophysis both in patients with tuberculous and non tuberculous disease of the adrenal glands has been described Atrophy and lymphoid infiltration of the thyroid gland have been observed in about one fourth of the cases examined post mortem at the Presbyterian Hospital New York Enlargement of the thymus gland was found at autopsy in 5 of 20 patients with tuberculosis of the adrenal glands and in 5 of 10 patients with atrophic disease in the same series There is a general tendency to lymphoid hyperplasia in Addison's disease perhaps most marked in those cases of non tuberculous origin The hearts of patients dying from Addison's disease often are abnormally small

There are no other pathological changes which are encountered with regularity in hypoadrenalism except for the deposition of melanin in the skin and mucous membranes

Symptomatology

The clinical picture of Addison's disease usually is characterized by the insidious onset and progressive development of weakness and prostration nausea and vomiting pigmentation and arterial hypotension This disease usually is chronic in nature and its advance often is slow On the other hand at times the tempo of the development of the symptoms is greatly accelerated Thus patients whose disease has apparently been mild and well controlled may in the course of 2 or 3 days attain alarming severity of symptoms or may even die Death under these circumstances usually is associated with the picture of dehydration and shock These acute increases in the severity of the disease are termed 'adrenal crises and constitute episodes of decompensated' adrenal insufficiency Compensation may again be established and the disease then may return to its former slow course In this respect Addison's disease bears a close analogy to diabetes mellitus In these metabolic disorders the disease which may be mild in nature often is associated with episodes in which the intensity of the pathological process is temporarily augmented either by a need for more hormone or a decrease in that which is liberated by the diseased endocrine structures

The *weakness* of Addison's disease is an expression of the two chief disturbances resulting from a decrease in adrenal cortical function i e disturbances in (1) electrolyte and water metabolism and (2) protein and carbohydrate metabolism This is demonstrated by the fact that salt alone will greatly improve the

general sense of strength and the fact that Ingle has shown that compound E exerts a greatly beneficial effect upon the work-capacity of the adrenalectomized rat The degree of weakness which usually is most marked in the early morning not only varies from patient to patient but varies strikingly in the same individual from mild fatigability to utter exhaustion and prostration as seen in crises The weakness is not of the type exhibited with paresis of muscle groups but is one in which muscular activity is associated with a generalized sensation of effort and exhaustion

Symptoms referable to the *gastrointestinal tract* occur almost invariably in the course of Addison's disease as do weakness and fatigability The *appetite* of the Addisonian patient is capricious and varies with the fluctuations in severity of the disease In perhaps 10 per cent of patients there is a real desire for salty foods *Anorexia* often is an early sign of decompensated cortical insufficiency As a crisis develops anorexia becomes more marked *Vomiting* occurs at some time in at least 75 per cent of patients In those patients whose disease is well controlled it may be wholly absent or may take place very infrequently On the other hand in a crisis there may be complete gastric intolerance and vomitus may assume a coffee ground character *Hiccough* is present frequently during crises *Diarrhea* in the experience of the writer is distinctly uncommon among patients with Addison's disease in contrast to the adrenalectomized dog in which bloody diarrhea is commonly present in advanced insufficiency The gastrointestinal symptoms appear to be related at least in part to electrolyte and water disturbances with the attendant dehydration and decrease in circulating blood volume since they are strikingly relieved by the parenteral administration of sodium salts and water Lack of hormones influencing carbohydrate and protein metabolism may play a part also It must be recalled in appraising the gastrointestinal symptomatology as well as that of weakness that tuberculous infection is present in more than two thirds of the patients and that this may contribute to the symptomatology

Disturbances of the circulation constitute an integral part of hypoadrenalism *Arterial hypotension* is one of the most characteristic features of Addison's disease In patients whose disease is sufficiently advanced to cause them to seek medical aid the systolic blood pressure usually is below 100 mm Hg When adrenal decompensation progresses the pressure falls still further and the pulse pressure is strikingly reduced Thus in severe crises blood pressure readings of 55/40 are not uncommon It must be emphasized that the blood pressure at the first visit or when the patient has been walking about, temporarily may attain normal levels or upon occasion elevated levels There may be momentary increases in blood pressure which recur even in the presence of severe crises and which are difficult to explain Thus the writer observed one patient in whom shortly before death the blood pressure rapidly rose to 160/90 and then in the course of a

few minutes again fell to its previous level of about 60/50 At autopsy the cortical and medullary tissues both were virtually completely replaced by tuberculous granulation tissue In patients who have had underlying hypertensive disease, the arterial pressure tends to maintain relatively normal levels in the presence of moderately severe adrenal insufficiency The *venous pressure* usually is normal even when advanced hypoadrenalism is present

A small and feeble *pulse* as described by Addison is a characteristic feature of the disease and is often present even in patients with only mild insufficiency *Acrocyanosis* involving chiefly the proximal portion of the finger nails often is associated with hypotension and a small pulse in Addisonian patients The *heart* often is small in patients with Addison s disease particularly in individuals whose disease has been of long standing and inadequately controlled The heart size decreases abruptly during crises and increases with recovery The *heart sounds* are naturally distant when hypotension is marked, and the heart rate often is increased *Electrocardiography* reveals changes in adrenal insufficiency The most characteristic abnormalities are decreases in voltage a tendency for the T waves to become low in amplitude or inverted with prolongation of the QT and PR intervals The changes in T waves are reversible and are thought to be related to the tendency for the serum potassium to be increased in hypoadrenalism *Breathlessness* on exertion often accompanies the disturbances in circulation The circulatory disturbances i e hypotension rapid heart rate, small heart feeble pulse and cyanosis are, at least in part the result of the disturbances in electrolyte and water metabolism which result in a decrease in circulating blood volume, since they are alleviated to a great extent by the administration of salt and fluid It is possible that metabolic disorders referable to proteins and carbohydrate also play a part

Autonomic Regulation — It is indicated elsewhere that a number of patients die in adrenal crises indistinguishable from those related to salt and water depletion but without any significant abnormality in the concentration of sodium or glucose in the blood and without evident hemoconcentration These episodes may occur spontaneously in association with unexplained fever or following a surgical procedure It seems probable that they are related to a disturbance in autonomic regulation not controlled by the therapeutic agents now available This view receives support from the observations of Perera Perera has shown that Addisonian patients in apparent good health under treatment with desoxycorticosterone who have normal blood pressure blood volume and blood sugar, are highly sensitive to 2 5 mgm of acetyl beta methylcholine given subcutaneously The reaction can be inhibited by atropine but not by epinephrine Whether the increased sensitivity of the Addisonian patient to acetyl beta methylcholine is dependent upon cortical or medullary insufficiency has not been established

Pigmentation is the most typical objective clinical manifestation of Addison s

disease It is often noted first by friends and relatives of patients and patients not infrequently first seek medical aid because of its appearance

Indeed the writer has had two colored patients whose initial complaint was that they had turned several shades darker Another patient a white female complained that she had been unable to scrub her knuckles clean for some months In rare instances pigmentation may be present for 10 or 15 years before the other manifestations of hypoadrenalism become obvious On the other hand there are patients in whom the disease follows its usual course and who at no time develop pigmentation

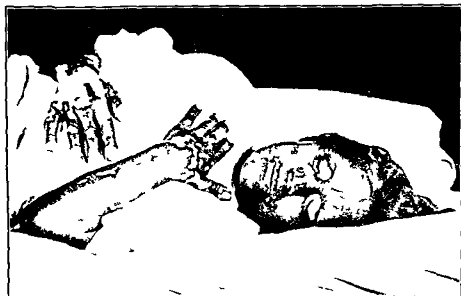


FIG 3 Simultaneous occurrence of pigmentation and depigmentation in a patient with Add son s d ease

The skin pigmentation in Addison s disease is brownish in color and is extremely variable in its intensity and distribution There may be generalized pigmentation and patients may become fully as dark as Fast Indian races On the other hand the increase in skin color may be difficult to recognize except for its intensification on pressure points and the genitalia and the areolæ of the breasts The color of pigmented nevi is greatly intensified even when generalized pigmentation is scarcely recognizable Occasionally pigmentation is blotchy in its distribution and may appear first as an area of discoloration of the forehead cheek or neck Occasionally deep and generalized pigmentation occurs in association with vitiligo as first depicted by Addison (Fig 3) The most characteristic pigmentation in

Addison s disease is that involving the mucus membranes of the oral cavity In this region the color is bluish black or brown, and the involved areas appropriately termed ' ink spots may involve the lips, gums, buccal mucosa or the tongue The gradual disappearance of pigmentation in a number of patients treated over the course of years with either salt or desoxycorticosterone has been commented on elsewhere

Loss of weight to some degree is almost always present and is naturally accentuated during crises when loss of salt and water through the kidneys is accentuated as are anorexia and vomiting It must be emphasized also that the underlying tuberculous infection, present in about three fourths of the patients, contributes to weight loss and other manifestations of hypoadrenalism[31] Despite the fact that loss of weight constitutes a part of the clinical picture of Addison's disease, cachexia rarely is marked

Abdominal pain without any distinguishing features is present at times Thus in the writer s series patients with established Addison's disease have been admitted to the hospital with diagnoses of gall bladder disease, peptic ulcer or malignancy of the gastrointestinal tract

Transient neurological disorders are not uncommon in patients with decompensated hypoadrenalism The changes cover a wide range and include confusional states, behavior changes or focal reflex disorders e g Babinski reactions clonus hyperreflexia, etc The *electroencephelogram* also shows abnormalities without any particular diagnostic pattern but often shows predominance of slow rhythm as seen in the hypoglycemic state The neurological disorders may be explained in part by hypoglycemia Whether disturbances in intermediary protein or carbohydrate metabolism also are factors is conjectural at present

Fever may or may not be present over long periods of time in Addisonian patients with tuberculous infection of the adrenal glands In patients whose disease results from primary atrophy of these structures it is present only during crises An abrupt rise to 104° or 105° F often appears as a terminal event without evidence of infectious disease to which patients with Addison's disease are reputed to be particularly susceptible Hypothermia in patients in contrast to adrenalectomized animals is not characteristic of hypoadrenalism although patients are particularly sensitive subjectively and objectively to exposure

Laboratory Tests

Examination of the *blood* of patients first presenting themselves for treatment usually shows no abnormality When a crisis is present there is usually an increase in red cells to about 5 5 million per cu mm and the hematocrit is increased Under treatment with desoxycorticosterone an underlying normocytic or secondary anemia becomes manifest as a result of hemodilution The red count however,

rarely falls below about 3 3 million per cu mm There are no characteristic changes in the white or differential blood counts although a mild degree of lym phocytosis often is present The erythrocyte sedimentation rate usually is in creased moderately in patients whose disease is due to tuberculosis During crises the sedimentation rate of patients with adrenal atrophy also is frequently elevated to 40 or 50 mm per hour The *urine* reveals no abnormality other than a general decrease in renal function as evidenced by a tendency to low fixation of specific gravity With patients under treatment with desoxycorticosterone Talbott has shown with careful studies of inulin and diodrast clearance that a decrease in the filtration fraction persists for at least many months

Chemical examination of the blood reveals changes dependent primarily on the degree of cortical decompensation at the time In the well controlled case no abnormalities of electrolyte metabolism may be apparent On the other hand mild *hypoglycemia* is present in most cases regardless of the state of their elec trolyte metabolism Thus among a group of 23 of the writer s patients the fasting blood sugar at some time was found to be below 80 mgm per 100 c c in 16 in 9 it was below 70 mgm and in 5 there were classical hypoglycemic episodes with blood sugar levels below 50 mgm per 100 c c

In untreated patients with low grades of uncompensated adrenal insufficiency the *blood sodium* often is 10 to 15 milli-equivalents below the normal level of 140 milli-equivalents per liter During crises the sodium concentration may fall still lower and reach 100 milli equivalents per liter As stated elsewhere this decrease in serum sodium is accompanied by an equivalent fall in *chloride* or *bicarbonate* or both but decreases in the chloride ion usually are greater than those in bicarbonate The *potassium* ion concentration of the blood serum is almost invariably normal except when the serum sodium is decreased During crisis some increase in potassium is present almost always and in rare instances the normal concentration of 4 to 5 milli-equivalents per liter may be doubled When renal function becomes impaired in the course of severe adrenal insufficiency some degree of nitrogen retention is observed Occasionally the non protein nitrogen of the serum may reach 100 mgm per 100 c c but levels exceeding 60 mgm per 100 c c are unusual No other chemical changes are observed in the blood with regularity in Addison s disease

The *basal metabolism* in patients with hypoadrenalism is often slightly de creased but in the writer s experience it is unusual to find levels below — 20 per cent

Course and Prognosis

The natural course of Addison s disease is one of slow progression in which the tempo may be temporarily increased or the disease terminated by a fatal

crisis The duration of the disease is extraordinarily variable For example, in the writer s series is a patient who has been known to have increasing pigmentation over a period of at least 14 years and whose disease still is easily controlled either by large doses of sodium chloride or small doses of desoxycorticosterone On the other hand the underlying hypoadrenalism may be well compensated, and the disease may remain unrecognized until perhaps a rapidly fatal crisis is induced by an acute infection a surgical procedure, a gastrointestinal upset severe emotional strain or the withdrawal of salt from the diet for any reason In a certain number of individuals sudden death may terminate the disease previously unrecognized and of unknown duration There is a general tendency for Addison s disease to be more rapidly fatal in cases due to tuberculosis than in cases due to primary atrophy of the adrenal glands This is borne out by 32 cases studied post mortem at the Presbyterian Hospital in New York In this series the average duration of life from the time of recognizable onset of symptoms in the cases due to tuberculosis was 28 months The duration of life in patients with primary atrophy was 53 months It must be recognized that tuberculosis itself takes its toll quite apart from the accompanying hypoadrenalism and the development of widely disseminated tuberculosis is not unusual

The advances in therapy in recent years have greatly modified the outlook for the duration of life Thorn has compared the mortality rate in patients with Addison s disease prior and subsequent to the use of specific therapy He finds that the mortality rate at the end of 1 5 years prior to specific therapy was about 63 per cent Since the introduction of salt and desoxycorticosterone treatment the mortality rate after 1 5 years has been only 16 per cent It is the writer s impression that the prognosis in Addison s disease is, in general not as good in women as in men particularly among patients under treatment with desoxycorticosterone It is sudden death presumably of cardiac origin which appears to predominate in females This coincides with Thorn's finding that abnormalities in the electrocardiogram are more frequent in women than in men with the disease

It seems probable that the prognosis for patients suffering from hypoadrenalism will be greatly improved when steroids possessing effects on protein and carbohydrate metabolism are made available Whether these steroids will prove effective against the autonomic disturbances which at present contribute to the fatal termination of Addisonian patients cannot be anticipated

Diagnosis

The diagnosis of Addison s disease can be inferred with a measure of confidence in patients presenting a history of progressive asthenia nausea vomiting increasing pigmentation particularly when it involves the buccal mucosa and

arterial hypotension The presence of tuberculous infection involving the urogenital tract or the bones adds support to the diagnosis On the other hand the diagnosis often is entirely unsuspected in patients in whom only mild pigmentation or no pigmentation is present but in whom symptoms of fatigue and anorexia are ascribed either to a neurosis or to an exhaustion state Addison s disease also escapes recognition in patients whose disease is well compensated and who have no definite symptoms until a severe or fatal crisis follows a surgical procedure a gastrointestinal upset infection or the withdrawal of salt from the diet

In patients with recognizable pigmentation Addison s disease must be differentiated from other disorders associated with brownish pigmentation These include hemochromatosis chronic biliary tract disease with low grade intermittent icterus prolonged cachexia with or without neoplasia dermatomyositis and scleroderma vagabond s disease (chronic pediculosis) ochronosis chronic poisoning by arsenic or silver prolonged uremia certain blood dyscrasias in which asthenia and changes in skin color are prominent and very occasionally hyperthyroidism associated with pigmentation Addison s disease must be differentiated also from anterior hypophyseal insufficiency as characterized by Simmonds disease

The greatest and most frequent difficulty is found in the differentiation between unpigmented patients with true hypoadrenalism and patients suffering from exhaustion states or chronically fatigued individuals with or without neuroses These patients complain more bitterly of fatigue and exhaustion as a rule than do many patients with outspoken hypoadrenalism Hypotension also in these patients is at times persistently more marked than in Addisonian patients except in a severe crisis At the same time these patients despite protestation are capable of more sustained physical activity than are patients with demonstrable hypoadrenalism

It is often suggested that this group of tired and exhausted human beings suffer from *functional hypoadrenalism* There is at present little evidence to support this viewpoint The observation that the adrenal glands show evidence of increased activity in response to various forms of stress and the reputed appearance of steroids with adrenal like activity in the urine of patients subjected to stress are suggestive This evidence does not indicate however that an insufficient quantity of the adrenal cortical steroids is liberated from the adrenal glands Indeed chemical studies of the blood of chronically fatigued and exhausted individuals fail to reveal the changes characteristic of hypoadrenalism although the symptoms may be extreme

In patients with Addison s disease of tuberculous origin x ray examination of the adrenal area may prove of help in establishing the diagnosis since calcification in one gland or more frequently in both glands is often present On the other hand the presence of demonstrable calcification in these structures does not

establish the presence of hypoadrenalism For example the writer has seen two children between 9 and 11 years with marked calcification of the adrenal glands who had no demonstrable evidence of Addison s disease

The diagnosis of hypoadrenalism suspected on the basis of clinical observation, at the present time can be established with certainty by *laboratory methods* only through the demonstration of a defect in electrolyte and water metabolism Defects in carbohydrate metabolism as demonstrated either by a low fasting blood sugar level a low and flat glucose tolerance curve or by increased sensitivity to insulin are not specific in the absence of a demonstrable defect in sodium metabolism and offer only corroborative evidence for the diagnosis Furthermore testing insulin sensitivity in an Addisonian patient is not justifiable as it is attended by danger to the patient s life without yielding significant information

When the *sodium concentration* of the blood serum is found to be below 136 milli-equivalents per liter and when there is no apparent reason for loss of base from the body, the diagnosis of hypoadrenalism must be seriously entertained It must be emphasized, however that depression of the blood sodium level occurs frequently with severe diarrhea, upper intestinal obstruction with marked vomiting fistulous openings in the small bowel, uremia severe infection particularly when associated with extreme sweating, and diabetic acidosis In a few instances the level of sodium in the serum is depressed in severe cachectic disease without anatomical evidence of hypoadrenalism An increase in serum potassium concentration, which accompanies a fall in sodium and a rise in non protein nitrogen adds to the certainty of diagnosis

The concentration of sodium in the blood serum is normal in patients whose Addison s disease is either mild or compensated by a large intake of the sodium ion In these patients the diagnosis of significant hypoadrenalism can be established only by subjecting the sodium metabolism to abnormal strain

The following three tests which place a strain upon sodium metabolism are employed for the diagnosis of compensated or latent adrenal insufficiency

(1) *Salt Deprivation Test* — This procedure is exceedingly simple and yields results which are perhaps more conclusive than are the results of the two other procedures described next The salt deprivation test should never be employed in a patient suspected of Addison's disease whose serum sodium level has already been shown to be below normal The test also should never be carried out without having the patient under close observation in a hospital

The technique of the test is as follows The patient after a preliminary determination of the serum sodium non protein nitrogen and glucose concentrations is given a regular salt poor diet containing less than 1 0 gram of sodium daily The patient s symptoms and appearance are noted carefully, and the blood pressure is determined twice daily On this restricted diet the symptoms of hypoadrenalism develop as a rule in 3 to 6 days but may attain alarming pro-

portions in some cases within 24 hours When marked anorexia appears or vomiting begins the test should be discontinued at once Also if the degree of exhaustion accelerates rapidly the pulse volume decreases notably and the arterial systolic pressure begins to fall below 85 blood should be taken for the determinations mentioned above and treatment should be instituted immediately If significant hypoadrenalism is present, the blood sodium * under the conditions of the test will fall below 133 m eq per liter and there may be an increase in non protein nitrogen If the subjective and objective manifestations of acute adrenal insufficiency do not appear in the course of 6 days of a salt poor diet it is highly improbable that a patient's complaints can be ascribed to hypoadrenalism When the salt deprivation test is completed with the appearance of symptoms the patient is greatly benefited by the prompt infusion of 1 500 c c of 5 per cent glucose in physiological saline

(2) *Cutler Wilder and Power Test* — This test is based on the determination of the concentration of chloride found in the urine after the patient has been maintained for 3 days on a measured diet containing a small amount of sodium and a high content of potassium The fluid intake is restricted during the test The application of this procedure is attended by the same grave danger to the patient as that presented by the salt deprivation test Furthermore it is more complicated than is the latter test and the rapid development of adrenal insufficiency under the dietary restrictions imposed may lead to severe adrenal insufficiency before the completion of the test

(3) *Robinson Power and Kepler Test* — This test has an advantage over the two described in that the patient is not subjected to a procedure which entails the dangers inherent in the foregoing tests On the other hand the response of the patient as determined in the Robinson Power and Kepler test is far less specific for adrenal insufficiency than is the response to the salt deprivation test Consequently in the equivocal case the writer recommends the salt deprivation test The Robinson Power and Kepler test involves two procedures one based upon the volume of urine excreted in a given period of time the other upon the relationships between the concentrations of urea and chloride in urine and blood plasma in relation to urine volume e g in the Addisonian patient the reabsorp-

* When laboratories are not equipped for the routine determination of serum sodium the calculated sodium may be employed The sodium is calculated by the addition of the CO_2 content expressed as m eq per liter and the Cl concentration of the serum expressed as m eq per liter plus 10

Example	Serum CO_2	= 26 2	m eq per liter
	Serum Cl	= 103 8	m eq per liter
		+10 0	
		= 140 0	m eq per liter

This type of determination is extremely accurate except in the presence of PO_4 and SO retention or in the presence of marked ketosis or after exercise when lactic acid in the blood is greatly increased

tion of chloride and water is decreased and the excretion of urea is decreased, possibly because of a diminution in renal blood flow

It has been suggested at various times that the diagnosis of Addison s disease can be established by the therapeutic trial of salt solution or various preparations of adrenal cortical hormones This viewpoint is not valid An individual with depletion of inorganic base may be benefited by the administration of salt and water regardless of the nature of the underlying cause Likewise the administration of desoxycorticosterone esters may cause retention of salt and water in conditions other than adrenal insufficiency

The subjective improvement reported following the injection of adrenal cortical extract probably is psychological in many instances and consequently has no diagnostic significance in these patients

Treatment

The treatment of Addison s disease should be directed primarily toward the correction of the physiological disturbances which develop as a consequence of the endocrine deficiencies present The nature of the therapy and the vigor with which it must be applied naturally vary tremendously with the severity of the disorder For example in the individual whose disease is well compensated a few general measures, including moderate regulation of the diet, the ingestion of a liberal amount of salt the avoidance of physical and mental fatigue and the immediate care of even mild acute infections may suffice to maintain comparatively good health over periods of months or years Thus the writer has three patients with well established Addison s disease who still, after periods of nine seven and three years respectively are able to carry on their occupations and gain their livelihood by observing these simple safeguards On the other hand with the gradual progression of the disease or with the appearance of a crisis more active therapeutic measures must be applied Indeed, failure to institute active and intensive therapeutic measures promptly may, at times needlessly sacrifice patients who otherwise might be restored to an active and useful existence

The recent advances in the treatment of Addison s disease are reflected in the great increase in life expectancy as previously mentioned Progress made has been achieved primarily through the correction of disturbances of electrolyte and water metabolism by means of the introduction of salt and desoxycorticosterone esters as therapeutic agents Unfortunately equal progress has not been made in the treatment of the disorders dependent upon the disturbances in protein and carbohydrate metabolism present in hypoadrenalism This may explain in part the fact that a number of patients with Addison s disease die in crises while under treatment with salt or desoxycorticosterone and in spite of adequate control of electrolyte metabolism

The patient in whom the diagnosis of Addison's disease has been established should remain in a hospital for the initiation of therapy. This is essential because the type of treatment which the patient will have to carry out subsequently depends upon clinical and laboratory information which can be obtained only with the patient under observation. The first and foremost decision to be made is whether specific hormone therapy is indicated or whether the disease can be controlled satisfactorily by the regulation of the sodium intake alone. If a crisis is present immediate treatment with hormone is indicated as described below. If on the other hand symptoms are of only moderate intensity and the level of blood sodium is not below 130 m eq per liter a trial of salt therapy alone is indicated. Salt therapy may be tried also for maintenance of the patient after the disturbances in electrolyte metabolism have been corrected by the use of hormone with or without the addition of salt in excess of that present in the diet.

The control of the *diet* in the treatment of hypoadrenalism no longer requires great emphasis. Perhaps the best general guide is to allow the patient to follow his desires. If nausea is persistent a temporary reduction in food bulk is advisable. If anorexia is persistent salt therapy should give way to treatment with cortical hormone. If tuberculosis is present a particular attempt should be made to improve nutrition. Before desoxycorticosterone esters became available the theoretical advantage of a diet low in its potassium content was properly emphasized by Wilder. Today the low potassium diet has no place in the treatment of Addison's disease. The patient who cannot be maintained in good health with salt therapy must be treated with desoxycorticosterone. Moreover in treatment with desoxycorticosterone a low potassium diet may lead to further abnormal depression of the serum potassium level which tends to be low because desoxycorticosterone increases the urinary excretion of this ion even in the presence of a normal diet.

The most important dietary consideration is that related to the carbohydrate intake. The frequency of *hypoglycemia* in Addison's disease has been indicated. It should be stressed that this manifestation appears to occur more frequently in patients treated with salt and desoxycorticosterone than in untreated patients. This may result from the fact that these patients are more active than untreated patients and the underlying latent defect in carbohydrate and protein metabolism therefore becomes more apparent. It may be that treated patients live longer and thus the carbohydrate and protein disturbances have time to develop whereas the untreated patient is apt to die earlier from salt and water loss during a crisis. Be that as it may a patient who has once had a hypoglycemic episode is subject to recurrences. For this reason all Addisonian patients like insulin treated patients with diabetes should carry sugar for emergencies and should be instructed in the clinical manifestations of hypoglycemia. They should remember when in doubt about symptoms take a glass of orange juice or milk or at least

two lumps of sugar' Patients, who have been hypoglycemic, should be advised to eat bread or other carbohydrate between meals and at bed time to order to avoid further difficulty

Technique of Salt Treatment — When the diagnosis of moderately severe hypoadrenalism has been established, improvement of the patient is greatly expedited by the immediate administration of an infusion of 1,500 c c of 0 85 per cent sodium chloride solution in 5 per cent glucose During this first day of treatment the patient should be given also one gram of salt (sodium chloride) by mouth approximately every two hours for six doses On the second day the infusion may be repeated, if considerable subjective and objective improvement has not taken place The daily oral administration of salt is increased to 12 grams, given in 2 gram doses on the second day This dose of salt in addition to that of the diet then is maintained for the next 3 to 5 days At the end of this time the patient s appetite should be much improved, nausea should have disappeared, and there should be a striking increase in strength and in feeling of well being The pulse volume should be increased but the systolic blood pressure with the patient at rest may remain at this time at a level of about 95 mm Hg If improvement of the type described has not been achieved in the course of a week, it may be assumed that treatment with desoxycorticosterone esters will be necessary to attain a maximal therapeutic effect

After it has been ascertained that 12 grams of salt daily restore the blood sodium level to normal, an attempt may be made to reduce the salt allowance gradually However most patients require this dose The ingestion of the amounts of salt necessary for maintenance of the patient is best accomplished in most cases by the administration of sodium chloride in 1 gram enteric coated tablets A few patients prefer to dissolve one half teaspoonful (2 grams) of salt in a tumbler of water In patients requiring 12 grams or more of salt in addition to that of the diet nausea or mild diarrhea may ensue If salt is not tolerated treatment with cortical hormone is indicated It has been suggested by Wilder and his associates that sodium chloride should be supplemented with sodium bicarbonate or citrate to avoid the development of "chloride acidosis in the course of salt treatment In the writer s experience this precaution has never been found to be necessary

Technique of Desoxycorticosterone Treatment — Desoxycorticosterone usually is given as the acetate although the propionate is equally effective This synthetic cortical hormone usually is administered in one of the three following ways (1) by subcutaneous injection in peanut oil or sesame oil (2) by the subcutaneous implantation of pellets of the hormone and (3) by sublingual instillation of desoxy corticosterone esters dissolved in propylene glycol Subcutaneous administration in a beeswax medium has been employed also

Each method has its special advantages as well as its limitations Any one

of these routes may be employed for the maintenance of the patient, but the amounts required for sublingual use as devised by Anderson add greatly to the cost of therapy and the careful control of dosage at times is difficult The implantation of pellets for the continued care of the patient has the obvious advantage that the patient does not have to be concerned with daily treatment either by injection or by sublingual instillation of hormone On the other hand the dangers of overdosage with the implantation of pellets are apparent particularly in patients in whom there are wide fluctuations in hormone requirement To avoid this complication of pellet implantation underdosage is advisable For this reason the majority of patients with implanted pellets require supplements of sodium salts for their maintenance and at times subcutaneous injections of hormone as well The daily subcutaneous injection of hormone demands that the patient learn the technique involved With the subcutaneous injection of desoxycorticosterone the hormone dosage is easily adjusted to the needs of the patient There are three disadvantages of the subcutaneous route of administration First the amount of hormone required is greater and consequently the cost is greater than when pellets are implanted, second there are dangers of abscess formation from inadequate sterilization third a few of the patients develop persistent subcutaneous induration from their injections In the opinion of the writer the choice between pellet implantation and subcutaneous injection of hormone should at least in part be left to the patient In any event desoxycorticosterone therapy always should be initiated with subcutaneous injections in order to determine the patient s hormone requirements In patients with tuberculosis pellets should not be implanted until fever has subsided at which time the requirements can be established satisfactorily

Subcutaneous Injection Method — The daily maintenance dose of desoxycorticosterone acetate given by subcutaneous injection varies between 1 and 7 mgm depending upon the severity of the disease When desoxycorticosterone therapy has been decided upon either on a priori grounds or because satisfactory improvement has not resulted from salt treatment alone 10 mgm may be given on the first and second days and then unless symptoms are severe subsequent daily injections of 5 mgm are administered The serum sodium should be determined at intervals of about 5 days or oftener if progress is not satisfactory If the sodium returns to normal and the patient s strength continues to improve the dose may be reduced 1 mgm at a time at intervals not more frequent than once a week to determine the minimum requirement If the sodium does not return to normal the daily dose is increased gradually

If hormone treatment is to be substituted in a patient who has been receiving 12 or more grams of salt in addition to that in his food the therapy may be initiated as follows desoxycorticosterone treatment may be instituted as described or the patient may be given 3 mgm of hormone and 6 grams of added salt daily

for 3 to 5 days. Subsequently the dose of hormone may be increased at a rate of 1 mgm. at 5 day intervals with simultaneous decreases of 3 grams in the salt ration. The continued administration of more than 10 mgm. of desoxycorticosterone coincident with large doses of salt leads, at times, to excessive retention of salt and water with complications discussed elsewhere.

If an Addisonian patient is given adequate amounts of desoxycorticosterone, salt need be given only according to taste. On the other hand the daily requirement of hormone can be diminished appreciably, as is indicated in the above outline of treatment, if the ingestion of sodium chloride is increased. For example, a patient, whose desoxycorticosterone requirement is 6 mgm. daily, may be maintained in equally good health by the administration of 3 mgm. of hormone supplemented by 6 grams of sodium chloride. This is a point of practical importance for many patients because of economic reasons.

A number of matters of detail concerning the subcutaneous administration of desoxycorticosterone deserve mention. The patient should be taught to inject the hormone himself. The anterior crural regions serve as the best site for injection, and the patient should be advised not to use the same site on repeated days. The area should be massaged for 5 minutes after injection; this decreases the incidence of induration. The patient, whose maintenance requirements of desoxycorticosterone acetate are being determined, should be weighed daily. If the rate of gain, due primarily to salt and water retention, after the first 3 days of treatment exceeds about one half a pound daily, the dose of hormone or of salt should be reduced.

Implantation Method. — The treatment of hypoadrenalism by the implantation of pellets of desoxycorticosterone acetate has been developed chiefly by Thorn, and the following procedure is essentially that outlined by him. Before pellets are implanted, the maintenance dose is determined by subcutaneous administration as described above. These patients during this time should receive a supplement of 3 or 4 grams of salt daily in addition to that of their diet. The average time required for assay on this basis is about 4 weeks. The patient then should resume activity for another month to be certain that the optimum dose has been determined as judged by the fact that the blood sodium remains at a normal level and clinical improvement is sustained. Then one 125 mgm. pellet of desoxycorticosterone acetate is implanted for each 0.5 mgm. of hormone found to be required by daily injection. The pellets are implanted subcutaneously in the infrascapular regions. These pellets are effective in most patients for about one year. When they have almost dissolved, symptoms of hypotension, anorexia and weakness gradually reappear. New pellets may be implanted as these symptoms increase.

The technique of manufacture of the pellets is of great importance. If they are too soft, they may crumble with the rapid absorption of hormone which

may result in severe overdosage On the other hand if they are packed too firmly the rate of solution may be markedly diminished and consequently their effect may be reduced

If satisfactory improvement does not take place after pellets are implanted the intake of sodium chloride should be increased Approximately 50 per cent of Thorn's patients who have had pellets implanted require a supplement of 3 or more grams of salt daily If symptoms of overdosage of cortical hormone appear pellets should be removed promptly Potassium chloride in doses of 1 5 grams daily may be given until the pellets are removed

Results — The results of desoxycorticosterone therapy are shown in part in Fig 2 The clinical improvement often is striking The majority of patients are restored to health compatible with earning their livelihood and the effects of this type of treatment upon the mortality rate have been commented upon The blood pressure increases slowly but the normal level may not be attained for many weeks in some patients despite improvement in other directions

It is the writer's opinion that supplements of 5 or 10 c c daily of the commercially available aqueous *extracts of the adrenal cortex* are of little or no benefit in the maintenance of the patient with Addison's disease These doses prevent hypoglycemia in the rat and dog but they are not of demonstrable value in man A lipo-extract of hog adrenal glands has been prepared and according to Ingle 1 c c contains the equivalent of about 4 mgm of corticosterone when assayed by the work capacity of the adrenalectomized rat This preparation in man demonstrates salt and water activity and can be shown to increase nitrogen excretion presumably as a result of its effect on protein metabolism It increases the subjective feeling of well being significantly in patients with Addison's disease

Treatment of an Adrenal Crisis — Adrenal crises develop in the course of Addison's disease at various times for reasons which have been discussed When a crisis appears vigorous therapy should be initiated at once Treatment should be directed towards the correction of (1) shock which is dependent upon a decrease in circulating blood volume and which results from loss of sodium salts and water and (2) the prevention of hypoglycemia The first of these disorders is corrected by the administration of salt and water in conjunction with desoxycorticosterone The second may be avoided by the repeated administration of glucose and at least theoretically by the liberal administration of adrenal cortical extract which is known to contain small quantities of steroids which increase gluconeogenesis or inhibit carbohydrate oxidation or both

The patient should be kept warm and a blood sample should be taken for the determination of sodium glucose non protein nitrogen and serum protein concentrations An infusion of 1 500 c c of 5 per cent glucose in 0 85 per cent sodium chloride solutions (not Ringer's solution) should be given immediately

This should be repeated depending upon the condition of the patient with particular emphasis upon the blood pressure as a criterion If the pressure remains below 80 mm Hg an infusion of 1,000 c c of plasma or a transfusion of blood should be given slowly or the infusion of glucose in saline should be repeated in 4 to 6 hours Even if the patient s condition is not critical the initial infusion should be repeated on the first day after 8 to 12 hours Following this a daily infusion should be given until vomiting has stopped the appetite is improved and the temperature has returned to normal If tuberculosis associated with fever is present infusions naturally are to be continued only until the blood sodium returns to approximately normal levels In patients, who develop hypoglycemia a hypodermoclysis of 1,000 c c of 5 per cent glucose solution injected with large amounts of novocaine may serve as a reservoir for sugar and may prevent a recurrence of hypoglycemia until small feedings of milk or diluted fruit juice with added sugar or lactose can be tolerated

In conjunction with the treatment with saline the patient in a crisis should be given 15 mgm of desoxycorticosterone intramuscularly immediately upon admission and 5 mgm more 6 and 12 hours later The sites of injection must be thoroughly massaged For the next two days 5 mgm of desoxycorticosterone may be given twice a day unless excessive fluid retention occurs Following this the patient s salt and hormone are adjusted as described for the maintenance of the patient

In a certain number of patients crises occur, which appear identical with those associated with the usual depletion of salt and water but the electrolyte pattern of the blood serum is found to be normal In these patients the blood pressure falls rapidly, the temperature rises abruptly without obvious cause and the patient frequently succumbs despite all therapy The nature of the disturbance in these patients is not clear but it may result from a disturbance in capillary permeability or in vasomotor regulation In the treatment of these individuals therapy with saline solution and desoxycorticosterone should be initiated as described above but after the first infusion and the first dose of desoxycorticosterone large doses of cortical extract should be administered at frequent intervals without further recourse to saline solution and desoxycorticosterone particularly in the absence of hemoconcentration Twenty to thirty c c of cortical extract should be injected intravenously and the patient should receive doses of 10 c c of cortical extract every 1 or 2 hours until the blood pressure rises above shock levels, and the temperature falls Transfusions of plasma or whole blood may be tried if progress is not satisfactory but the results usually are disappointing

In the opinion of the writer *injections of epinephrine* have no influence upon the outcome of the Addisonian crisis but they do not appear to have an adverse effect when given in small doses

Complications of Desoxycorticosterone Therapy — The effects of excessive doses

of desoxycorticosterone in the normal dog have been discussed elsewhere In patients with Addison s disease excessive dosage results in (1) edema and at times generalized anasarca (2) congestive heart failure and (3) arterial hyper tension

Extensive *edema* not infrequently was observed in the early days of desoxy corticosterone therapy when large doses of the hormone and salt were given over rather prolonged periods of time With the plan of therapy outlined above the appearance of significant edema is distinctly unusual If edema does appear it is controlled readily by a reduction in the intake of sodium salts or by a reduction in dosage of desoxycorticosterone in patients not receiving supplementary sodium chloride medication

Cardiac insufficiency like anasarca is today a complication rarely encoun tered in the course of desoxycorticosterone therapy It appears to result from a combination of an increase in plasma volume increase in arterial pressure and a decrease in concentration of potassium in the blood serum with a slight but similar decrease in the potassium of heart muscle cells in dogs Darrow has demonstrated histopathological lesions in the heart muscle of normal rats receiving large doses of desoxycorticosterone over long periods of time Similar changes do not de velop regularly in man The heart of the Addisonian patient is unusually small before treatment It returns to normal with well controlled therapy and dilates only if excessive salt and desoxycorticosterone are administered When heart failure occurs it is associated usually with dyspnea orthopnea pulmonary con gestion and an increase in venous pressure On the other hand sudden death apparently of cardiac origin but without congestive failure is encountered oc casionally in patients who have received large amounts of hormone Cardiac insufficiency should be treated by the cautious reduction in the dosage of hormone and salt Digitalis should be used as in other types of congestive failure

Arterial hypertension as stated elsewhere appears rather frequently in patients treated with desoxycorticosterone after 6 months to a year of treatment If the pressure does not exceed 150/90 little cognizance need be taken of this complica tion In patients who have had hypertensive disease prior to the onset of Addi son s disease the reappearance of significant hypertension may occur In patients who develop hypertension an attempt should be made to reduce the dose of salt or hormone or both without inducing manifestations of hypoadrenalism

Occasionally *contractures of the lower extremities* appear in patients receiving desoxycorticosterone therapy but it has not been demonstrated that these develop as a consequence of treatment with this hormone

Intercurrent infection constitutes a serious complication in Addison s disease perhaps because of failure of the immune mechanism as suggested by White and Dougherty and it commonly induces crises which not infrequently prove fatal When infection accompanied by fever occurs the patient should be hospitalized

This should be repeated depending upon the condition of the patient with particular emphasis upon the blood pressure as a criterion If the pressure remains below 80 mm Hg an infusion of 1 000 c c of plasma or a transfusion of blood should be given slowly or the infusion of glucose in saline should be repeated in 4 to 6 hours Even if the patient's condition is not critical, the initial infusion should be repeated on the first day after 8 to 12 hours Following this a daily infusion should be given until vomiting has stopped the appetite is improved and the temperature has returned to normal If tuberculosis associated with fever is present, infusions naturally are to be continued only until the blood sodium returns to approximately normal levels In patients, who develop hypoglycemia a hypodermoclysis of 1 000 c c of 5 per cent glucose solution injected with large amounts of novocaine may serve as a reservoir for sugar and may prevent a recurrence of hypoglycemia until small feedings of milk or diluted fruit juice with added sugar or lactose can be tolerated

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Complications of Desoxycorticosterone Therapy — The effects of excessive doses

identical with that of the surgical patient or of an Addisonian patient with in fection

Climate

Addisonian patients are particularly susceptible to extremes of heat and cold Crises are especially common during hot weather and may be precipitated by physical exercise associated with profuse sweating with consequent loss of sodium salts and water During hot weather patients should drink more water and increase their consumption of salt perhaps 2 or 3 grams if sweating is profuse They should be advised to avoid undue exertion at these times Many Addi sonian patients feel the cold intensely and should dress accordingly in winter Adrenalectomized animals die quickly when subjected to ice box temperatures perhaps because they are unable to convert protein to carbohydrate adequately under this form of stress

Pain and Mental Reaction

It is the impression of the writer that painful stimuli augment the manifesta tions of adrenal insufficiency and that for this reason they should be avoided as far as possible In most Addisonian patients codein is particularly well tolerated and should be used freely for the control of pain

Anxiety often intensifies anorexia nausea and gastric intolerance in the patient with Addison s disease For example in one of the writer s patients a university professor a fatal crisis appeared to be initiated by worry over a severe financial reversal

WATERHOUSE FRIDERICHSEN SYNDROME

For many years there have appeared in medical literature case reports of patients presenting a clinical picture which has come to be known as the Water house Friderichsen syndrome This disease picture usually is encountered in infancy or early childhood but is seen also in adults It deserves brief considera tion in this section since some of the manifestations may be ascribed to *acute cortical adrenal insufficiency* The Waterhouse Friderichsen syndrome is charac terized in most cases by the abrupt onset of fever headache delirium or convul sions nausea and vomiting These symptoms are associated with the development of a generalized purpuric rash in which the lesions vary from 1 mm to more than 1 cm in diameter Marked peripheral cyanosis appears as the disease progresses and the blood pressure falls to shock levels Patients usually succumb in 24 to 72 hours with the picture of profound circulatory collapse Extensive hemorrhage into the adrenal glands as determined at autopsy constitutes an integral part

at once, and an infusion of glucose in saline solution should be given immediately. Desoxycorticosterone or cortical extract should be given as in a crisis. Penicillin or sulfadiazine should be given at once and in full dosage whenever the infectious agent is one likely to respond to this type of therapy.

It must be reemphasized that tuberculous infection is present in the majority of patients suffering from hypoadrenalism. In these patients the treatment of tuberculosis constitutes an independent and important problem.

Surgery in Hypoadrenalism

Surgical procedures, particularly when associated with the administration of a general anesthetic, precipitate serious and frequently fatal crises. The introduction of desoxycorticosterone has reduced operative mortality appreciably in Addisonian patients. Nevertheless the surgical risk is great, and only the most essential operative procedures should be undertaken, e.g. operations for acute appendicitis, operations for mastoiditis and nephrectomy for tuberculosis, etc. Whenever possible, surgical procedures should be carried out under local anesthesia. When a general anesthetic is necessary, cyclopropane or open ether are to be preferred.

If operation can be delayed with safety, the patient should be given 10 mgm of desoxycorticosterone subcutaneously and an infusion of 1,500 c.c. of 5 per cent glucose in 0.85 per cent sodium chloride solution 6 hours before operation. The infusion should contain in addition 40 c.c. of cortical extract. At the time of operation, before anesthesia is started, this treatment should be repeated or 500 to 1,000 c.c. of plasma may be given. After operation the blood pressure should be followed at least every 2 hours and the same vigilance should be exercised as in the treatment of a crisis. Desoxycorticosterone should be given in doses of 10 mgm daily and 20 c.c. of cortical extract should be given subcutaneously or intramuscularly at 4 to 6 hour intervals for 2 or 3 days. Infusions should be repeated at 12 hour intervals if progress is not satisfactory.

Pregnancy in Addison's Disease

The severity of Addison's disease may be intensified in the first 3 months of pregnancy by nausea and vomiting. In the latter half of the period of gestation the disease may possibly be ameliorated by the secretion of the fetal glands and by the liberation of sex hormones which have been shown by Thorn and others to increase the retention of the sodium ion and water. At the time of delivery and in the first 2 or 3 days postpartum a serious and often fatal crisis may result from loss of fluid and blood as well as of progesterone and also circulating cortical hormone from the fetus. The treatment of the patient at the time of delivery is

fusion glucose in saline infusions desoxycorticosterone and cortical extract made a complete recovery without evidence of residual adrenal cortical insufficiency The part played by adrenal cortical therapy in the recovery of this patient obviously is wholly speculative It is conceivable that the chemical changes in the blood were nonspecific Nevertheless it seems proper in view of the demonstrable effects of infection on activity of the adrenal cortex to employ adrenal cortical replacement therapy in combination with specific chemotherapy for the underlying sepsis

Hypoadrenalism in Hemorrhage Traumatic Shock and Burns

The loss of a small amount of blood mild trauma and burns even small in area prove rapidly fatal to adrenalectomized animals The resistance of these animals to the injuries described is greatly enhanced by preliminary treatment with large doses of adrenal cortical extract As has been indicated animals and human subjects suffering from adrenal cortical insufficiency present numerous symptoms and signs identical with those present in the states of shock Furthermore the adrenal glands in fatal traumatic shock hemorrhage and burns show certain characteristic changes On the basis of these facts numerous experimental and clinical studies have been undertaken to determine the possible therapeutic value of adrenal cortical hormones in the disorders mentioned At the present time no convincing evidence has been adduced to indicate that the adrenal cortical hormones available have any significant value in the treatment of hemorrhage traumatic shock or burns in patients or in any but adrenalectomized animals

Hyperfunction of the Adrenal Medulla

Tumors of the medullary portion of the adrenal glands include gangliomata neuroblastomata and pheochromocytomata The first two of these are not associated with disturbances of adrenal function On the other hand the pheochromocytoma or paraganglioma induces in many instances a characteristic and dramatic clinical picture which results from the intermittent discharge of epinephrine into the blood stream

Pheochromocytomata may occur at any age but develop as a rule between the ages of 30 and 60 years They occur a little more frequently in females than in males The tumors vary considerably in size but are in most instances 2 to 4 cm in diameter and consequently can not as a rule be detected on physical examination The tumors arise most frequently from the pheochrome cells within the medulla of one adrenal gland In rare instances they develop in both glands Pheochromocytomata are found also arising from pheochrome cells in conjunction with the sympathetic ganglia elsewhere They have been reported also in the

of the syndrome but the syndrome may occur without the appearance of hemorrhage in the glands This syndrome is described also in Vol V, Chapt IV-A of Oxford Medicine

The Waterhouse Friderichsen syndrome develops as the result of overwhelming infection by any one of a variety of microorganisms The majority of cases are due to meningococcal infection, usually without meningeal involvement but the syndrome has been reported also in severe diphtheria and in sepsis caused by hemophilus influenza the pneumococcus, hemolytic streptococcus, etc It is believed also that a number of cases develop as a result of thrombocytopenic purpura In some of these cases however sepsis with depression of the circulating platelets may be mistaken for primary thrombocytopenia

In most instances the syndrome escapes recognition or the course is too rapidly fatal to permit studies which might help to clarify the role of hypoadrenalism in the state of collapse which terminates the disease However in one patient with fulminating meningococcus sepsis who presented the classical symptoms and signs of the Waterhouse Friderichsen syndrome chemical studies of the blood at the Presbyterian Hospital revealed the following information The serum sodium concentration was 122 9 milli equivalents per liter, the blood sugar was 50 mgm per 100 c c and the blood urea nitrogen was 58 mgm per 100 c c These changes are typical of cortical adrenal insufficiency and at autopsy extensive hemorrhage was found throughout both adrenal glands

The *treatment* of the Waterhouse Friderichsen syndrome should be directed toward (1) the control of infection and (2) the treatment of possible hypoadrenalism Penicillin or sulfadiazine should be used promptly and in full dosage The possible hypoadrenalism should be treated as an adrenal crisis In the case described above the level of sulfadiazine was maintained at 18 mgm per cent The patient was given repeated infusions of 5 per cent glucose in saline She was given 10 mgm of desoxycorticosterone upon admission and 5 mgm 6 and 12 hours later She received 40 c c of adrenal cortical extract intravenously and intramuscular injections of 10 c c of extract at frequent intervals Despite this therapy the patient, after temporary improvement became comatose, cyanosis increased and she died suddenly 72 hours after admission It is obvious that despite intensive and specific therapy treatment may be of no avail when the disease picture is well established It seems probable that generalized and irreversible tissue damage resulting from overwhelming infection was of greater importance in contributing to the fatal outcome of the Waterhouse Friderichsen syndrome in this patient than was acute cortical adrenal insufficiency In another patient with meningococcus sepsis and shock depression of the serum sodium to 121 m eq per l lowering of the blood sugar to 56 mgm per 100 c c and elevation of the urea nitrogen to 29 mgm per 100 c c were noted on admission to the Presbyterian Hospital This patient treated with penicillin sulfadiazine, trans

fusion glucose in saline infusions desoxycorticosterone and cortical extract made a complete recovery without evidence of residual adrenal cortical insufficiency The part played by adrenal cortical therapy in the recovery of this patient obviously is wholly speculative It is conceivable that the chemical changes in the blood were nonspecific Nevertheless it seems proper in view of the demonstrable effects of infection on activity of the adrenal cortex to employ adrenal cortical replacement therapy in combination with specific chemotherapy for the underlying sepsis

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carotid body In a boy of 12 years seen at the Presbyterian Hospital a large pheochromocytoma associated with intense and persistent hypertension was found in the adductor canal of the right thigh Epinephrine has been isolated from pheochromocytomata arising both within and without the adrenal glands on a number of occasions Pressor effects have not been observed in the tumors arising from the carotid body A large majority of pheochromocytomata are benign in character, but they may be malignant The malignant tumors rarely elaborate epinephrine

Clinical Picture — The clinical picture of hyperepinephrinism, as it occurs in association with pheochromocytomata, was described first by Labbe in 1922 The syndrome is characterized by terrifying and unpredictable episodes which vary from less than a minute to 1 or 2 hours in duration The sensations which the patient experiences as well as the objective findings, are those which ordinarily result from the injection of a large dose of epinephrine In the typical case the patient, either at rest or in association with some physical activity, is seized suddenly with a sense of constriction which often begins in the legs and arms and rapidly spreads to the epigastrium and the precordium This is followed quickly by a choking sensation The patient complains of terrific pounding of the heart and a throbbing headache, often associated with blurring of vision Nausea and vomiting occur frequently and the patient is aware of a coarse, uncontrollable tremor These symptoms are accompanied by a sense of great apprehension During the attacks there is striking pallor, the extremities are cool, the pupils tend to dilate, respiration is exaggerated there is usually an increase in pulse rate but bradycardia may be present The heart is over active, and in individuals with underlying heart disease pulmonary edema may develop The blood pressure rises during the attack, and the height of the pressure varies with the severity of the episode The systolic pressure, usually normal between attacks may rise to 300 mm Hg The diastolic pressure does not, as a rule, show a corresponding increase The blood sugar frequently rises in an attack from normal values to 160 to 200 mgm per 100 c c if the episode lasts for some time The hyperglycemia often is accompanied by transient glycosuria The attacks often are followed by a feeling of complete exhaustion which may last for many hours

The attacks usually are entirely irregular in their frequency even in the same individual Thus in one patient seen by the writer 4 attacks occurred in the course of 2 months and then the patient was entirely free from symptoms for 10 months Following this attacks increased in frequency, and in the course of the next year they occurred oftener than once a week The intensity of the attacks like their frequency is extremely variable and probably depends upon the amount of adrenalin discharged from the tumor at the time

In a few instances pheochromocytomata from which epinephrine can be extracted are associated with the presence of persistent rather than paroxysmal

hypertension The following record of a patient of Dr D W Atchley seen recently at the Presbyterian Hospital serves as an example The patient was a 29 year old unmarried school teacher whose blood pressure was found 2 years before admission to be 200/110 From that time on her pressure was persistently elevated while ambulatory and during a period of observation at another hospital 1 year before admission At that time when an attempt was made to ascertain the mechanism of her severe and sustained hypertension she complained of soreness in the right side of her abdomen and thought that a lump could be palpated For the year prior to admission she suffered from mild recurrent frontal headaches For 6 weeks before coming to the hospital she had had progressive failure of vision At no time had she had significant emotional disturbances nor had she ever experienced an episode suggestive of hyperepinephrinism On ophthalmoscopic examination the significant findings included mild but definite papilledema narrowing of the retinal arterioles old hemorrhages and exudate Her arterial pressure varied between 248/150 on admission and 200/100 after prolonged rest A fixed tender mass the size of a lemon was palpated to the right of the umbilicus At operation it was found to be attached to the vena cava During the manipulation of this mass in the process of its removal her blood pressure rose abruptly to 300/160 After almost complete removal of the mass the patient made an uneventful recovery and in the next 3 weeks her blood pressure at no time exceeded 145 mm Hg systolic or 100 diastolic The tumor proved to be a typical pheochromocytoma and preliminary pharmacological study has revealed the presence of a pressor substance presumably epinephrine

Diagnosis

The similarity of the state of panic which may occur in psychoneurotic patients under strain and attacks of hyperepinephrinism is apparent Consequently in patients with a history of marked emotional instability and a labile blood pressure the diagnosis of pheochromocytoma may be impossible or may become apparent only after a prolonged period of observation When however the typical disease picture appears suddenly and without warning in a patient without a background of instability the nature of the episodes should suggest at once the possible presence of a pheochromocytoma Careful observation of the sequence of events in an attack may help to differentiate an emotional panic from the hyperepinephrinism resulting from a pheochromocytoma Thus in the former the elevation of blood pressure heart consciousness and development of tremor follow the feeling of panic which results from a psychogenic stimulus In the patient with a pheochromocytoma the feeling of apprehension develops with the attack Furthermore in most instances the objective manifestations of hyperepinephrinism are greater than in the emotional state

In contrast to patients with hypertensive vascular disease it might be expected that patients with a pheochromocytoma would exhibit a decrease in skin temperature and a decrease in peripheral blood flow, characteristic of the action of epinephrine Evans and Stewart have observed just these changes in a patient studied by them One year after the removal of the pheochromocytoma they found an increase in the average skin temperature and in the peripheral blood flow These authors emphasize the fact that, whereas the average temperature of the hands and feet is decreased by the epinephrine secreted, there may be poor correlation between the skin temperature in the extremities and the average skin temperature at any one time

In a certain number of cases the diagnosis can be substantiated by the perirenal injection of oxygen by which the contours of the adrenal glands are made visible roentgenographically The presence of a tumor, which can not be palpated may become apparent with this procedure When a mass can be palpated in the abdomen and intermittent or persistent hypertension is present the mass may be massaged cautiously in order to reproduce evidence of hyperepinephrinism In the absence of a palpable mass or the demonstration of a tumor by perirenal air injection exploration to establish the diagnosis is often futile as the tumors may be multiple and may arise outside the adrenal glands but nevertheless is justifiable

Prognosis

The prognosis of patients with hyperepinephrinism is variable The disease may go on for many years with only occasional attacks On the other hand a patient may die during an episode particularly when associated with pulmonary edema

Treatment

Surgical removal of the tumor constitutes the basis of treatment This procedure carries with it however considerable risk Manipulation of the tumor in the process of its removal may cause the discharge of epinephrine with a serious rise in arterial pressure A number of patients have died suddenly during operation possibly as a result of ventricular fibrillation or acute cerebral ischemia During episodes of hyperepinephrinism sedatives should be administered and the patient should be placed in the semirecumbent position, if respiratory distress appears

Hyperfunction of the Adrenal Cortex

Hyperactivity of the adrenal cortex is associated with certain tumors of the cortex which usually are malignant and also with hypertrophy of the adrenal

glands which commonly is termed hyperplasia More frequently the disturbances which are ascribed to overactivity of the adrenal cortex are encountered in individuals who have no demonstrable gross or histopathological changes in the glands Hyperfunction of the adrenal cortex is manifested by two groups of disorders in which the physiological and clinical disturbances appear to result from the liberation of different steroids These two forms of hyperadrenalism are known as the *adrenogenital syndrome* and *Cushing s syndrome* Whereas the characteristics of each in pure form are fairly distinct in many instances certain manifestations of both syndromes occur in the same individual

Adrenogenital Syndrome

The adrenogenital syndrome as stated by Wintersteiner comprises all conditions in which the abnormal changes in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex The incidence of the syndrome is far higher in females than in males and in the former is characterized by the appearance of the secondary sex characteristics of the male with regression of the female characters In males the adrenogenital syndrome is characterized in children by precocious puberty and herculeanism and in adults it may result in a tendency toward feminization The age at which the adrenogenital syndrome develops is of the greatest importance in determining the degree of physiological and clinical change effected in the individual As a general rule it may be said that the earlier the onset in a patient the greater will be the deviation from normal development and appearance It is also of importance to recognize that the degree of physiological and clinical abnormality brought about by the adrenogenital syndrome bears no relation to the nature of pathological change in the glands Thus there may be none of the usual manifestations of the adrenogenital syndrome in a patient with a large and malignant tumor of the cortex and on the other hand the most extensive disturbances may appear without any demonstrable anatomical abnormality in these structures

It appears to be well established that the adrenal cortex is capable of elaborating both androgenic and estrogenic substances probably in response to chemical stimuli from the pituitary gland The significance of this type of activity in the adrenal glands under normal conditions is not apparent since the cessation of 17 keto-steroid excretion in the female with hypoadrenalism and a striking decrease in males with Addison s disease are not attended by any effect on the sexual activity of the individual Furthermore changes in growth and development which characterize the adrenogenital syndrome cannot be reproduced in animals by the injection of extracts of the adrenal cortex On the other hand certain of these changes can be simulated in young animals by the injection of androgenic or estrogenic substances and abnormalities can also be induced in the fetus by their

injection into pregnant animals It seems likely therefore that the development of the adrenogenital syndrome may be related (1) to excessive elaboration of normal or abnormal androgenic or estrogenic substances by the adrenal glands (2) to an abnormal degradation of adrenal steroids into active androgenic and estrogenic material possibly by the liver (3) to an increased responsiveness of certain body tissues to small amounts of normal or abnormal steroids elaborated by the adrenals or (4) to the elaboration of estrogenic or androgenic substances by other tissues e g arrhenoblastomata or granulosa cell tumors of the ovary

In the majority of patients exhibiting the adrenogenital syndrome there is an increase in the androgen content of the urine whether the syndrome develops in association with a cortical tumor or with hyperplasia, or whether it develops without anatomical change in the glands The nature of the androgenic material recoverable from the urine from patients with the adrenogenital syndrome varies and as already stated it may represent an abnormal steroid elaborated by the adrenal glands or an abnormal degradation product of a normal substance In a case reported by Dorfman and Schiller, an androgenic substance, androstenol 3 (α) 17 one was recovered from the urine The same material was isolated from the urine of another patient by Wolfe Fieser and Friedgood This androgenic compound showed no adrenal cortical activity when assayed in adrenalectomized rats In a number of cases the excretion of 17 ketosteroids may not exceed the accepted normal limits In these patients it is possible that the active principle is not eliminated in the ketonic form In other cases as stated elsewhere the individual may be unusually responsive to the normal steroids possibly on the basis of genic abnormalities Infrequently tumors of the adrenal cortex giving rise to the adrenogenital syndrome are associated with excessive excretion of estrogens instead of androgens

The adrenogenital syndrome may develop in utero or shortly after birth In female children of this age group the disease may possibly appear because of transmission of an excess of normal steroids from the maternal circulation The syndrome may develop also without any abnormal chemical stimulus from the mother In these infants the degree of deviation of the sex development from the normal is variable There may be only slight enlargement of the clitoris but more frequently well marked *pseudohermaphroditism* is present The clitoris may resemble a large penis there may be atresia or absence of the vagina and the internal genital organs may be quite rudimentary so that doubt may arise concerning the true sex In the male the appearance of the adrenogenital syndrome in utero or in infancy may result in pseudohermaphroditism with hypospadias and other changes simulating the external genitalia of the female if the disturbances in the steroid metabolism of the mother or fetus leads to the excessive production of estrogens

The excessive elaboration of androgens regardless of the basic cause i e, tumor etc in early childhood leads to excessive masculinization in both females and males In both sexes pubic and body hair appears frequently before the age of ten years the voice deepens acne appears on the face there is an unusual degree of muscular development the epiphyseal and dental development is accelerated and these children are extraordinarily alert mentally In the female the clitoris enlarges and in the male the genitalia are overdeveloped Sexual maturity appears in early childhood in males and menstruation may never appear in females This syndrome commonly is known as *adrenal virilism*

The appearance of the adrenogenital syndrome after puberty in the female is associated with a reduction or total cessation of the menses flattening of the breasts the development of hirsutism the appearance of acne deepening of the voice as a result of lengthening of the vocal cords and loss of normal libido In males the appearance of the adrenogenital syndrome is recognized only in those instances in which a tumor of the cortex is associated with the elaboration of estrogenic substances and a tendency toward feminization associated with enlargement of the breasts and hips and loss of libido

Diagnosis of Adrenogenital Syndrome — The appearance of the adrenogenital syndrome should lead to the suspicion of an adrenal cortical tumor or hyperplasia of the adrenal glands even though these abnormalities are present only occasionally Procedures which aid in the establishment of the diagnosis are (1) the determination of the 17 ketosteroid and estrogen excretion in the urine and (2) perirenal insufflation with oxygen to demonstrate roentgenographically the size and contours of the adrenal glands When doubt exists it may be justifiable to explore both adrenal glands It must be recognized that the adrenogenital syndrome may be simulated by virilizing tumors of the ovary e g arrhenoblastomata and granulosa cell tumors and that these must be excluded if possible by pelvic examination

Treatment — The treatment of the adrenogenital syndrome is surgical in cases in which tumor or definite adrenal hypertrophy is present Unfortunately the great majority of adrenal cortical tumors responsible for the syndrome are malignant although in certain instances the tumor can be diagnosed and removed before metastases occur In females who have reached puberty excision of the tumor may result permanently or temporarily in (1) re-establishment of menses (2) enlargement of the breasts (3) an increase in libido (4) a return of the voice to normal (5) the disappearance of acne (5) a decrease in 17 ketosteroid excretion and (7) some decrease in hirsutism Unfortunately the excess of facial hair, which constitutes one of the most distressing developments in these patients regresses but slightly in most instances In patients with significant bilateral adrenal enlargement without tumor resection of a portion of one or both glands usually brings about temporary alleviation of the disturbances mentioned In

the prepubertal group of patients with adrenal virilism the same diagnostic procedures and surgical treatment are indicated In addition, amputation of the enlarged clitoris and plastic operative measures may correct to some degree the anatomical abnormalities

In patients who are to undergo removal of an adrenal cortical tumor, or who are to have resection of an hypertrophied gland preoperative and postoperative treatment similar to that outlined for patients with Addison's disease is indicated In most of these patients there is comparatively little risk of acute adrenal insufficiency as compared with patients suffering from Cushing s syndrome, but this precautionary therapy nevertheless should be employed

In patients with the adrenogenital syndrome, in which tumor and hypertrophy of the glands have been excluded there is no treatment other than that which may be accomplished by plastic surgery or estrogenic therapy

Cushing s Syndrome

Cushing s syndrome was described first by Harvey Cushing in 1932 as a clinical entity which he found to be associated with basophilic adenomata of the pituitary gland Since the original observations made by Cushing it has been established that this syndrome usually appears without the presence of a basophilic adenoma of the pituitary Indeed it is most frequently associated with tumors of the adrenal cortex or hypertrophy of the adrenal glands and occasionally with tumors of the ovary It has been described also in association with thymic tumors and in a number of instances no tumors of endocrine structures have been found post mortem In almost all cases there appears hyalinization of basophilic cells in the hypophysis This was emphasized first by Crooke and it was suggested by him that this change might be related to the underlying mechanism involved in the development of the syndrome Heinbecker ascribes the development of Cushing's syndrome in a number of patients without either tumor or hyperplasia of the adrenal cortex to degeneration of the hypothalamic paraventricular nuclei This lesion is associated with Crooke s changes in the basophiles of the anterior lobe of the pituitary In these patients Heinbecker believes that Cushing s syndrome arises from an increase in responsiveness to the steroids normally elaborated by the adrenal cortex Experimental evidence believed to support this view is not wholly convincing The diversity of the disorders with which Cushing s syndrome or pituitary basophilism' may be associated suggests more than a single etiological basis It seems probable however that in all instances it may be referable either to over production of adrenal steroids or over responsiveness to normal secretions

Cushing s syndrome in most instances is associated with chemical, physiological and clinical disturbances which suggest hyperfunction of the adrenal cortex

In the adrenogenital syndrome as has been mentioned the disturbances present cannot be reproduced by the injection of adrenal cortical extract but can be simulated in part by the administration of androgenic and estrogenic hormones In Cushing s syndrome there is often an excessive excretion of 17 ketosteroids as in the adrenogenital syndrome but in addition more characteristic evidence of hyperfunction of the adrenal cortex usually is present Thus the concentration of the sodium in the blood serum is increased in many cases from the normal level of about 140 m eq per liter to 145 m eq per liter whereas the concentration of potassium may be reduced to about 3 5 m eq per liter These changes are both qualitatively and quantitatively similar to those induced in normal dogs by the prolonged administration of desoxycorticosterone Furthermore the tendency to lose nitrogen and the tendency to hyperglycemia and glycosuria resemble the effects produced either by the administration of cortical extract or steroids of the type of 17 hydroxy 11-dehydro-corticosterone to normal or partially pancreatectomized animals These effects can be induced also by the injection of anterior pituitary extract with its known diabetogenic activity Whereas these effects on carbohydrate and protein metabolism indicate that one action of these hormones is to convert protein into carbohydrate the assumption that this is the basis for the disturbances present in Cushing s syndrome lacks support It has been suggested by Albright that an excess of some cortical steroid which inhibits protein synthesis is responsible for many of the changes present in Cushing s syndrome This viewpoint which has much in its favor has not been established with any measure of certainty

Clinical Picture of Cushing s Syndrome — The clinical picture presented by patients with Cushing s syndrome is both striking and characteristic The syndrome occurs much more frequently in females than in males It may occur at any age but in contrast to the adrenogenital syndrome which usually appears under the age of 30 Cushing s syndrome is seen most frequently in women between the ages of 30 and 50 years The onset of the syndrome usually is insidious and the rate of progression is variable

The outstanding feature of Cushing s syndrome is the change which it effects in the appearance of the individual There is a tendency for the patient to become mildly or moderately obese although the distribution of fat and relaxation of the abdominal wall suggest a great gain in weight The cheeks become firm and shiny and tend to protrude giving a truly porcine expression The neck becomes thickened and appears short because of submental obesity The thorax and abdomen and hips also are sites of fat deposition The breasts become pendulous and the abdominal wall becomes relaxed protruberant and also pendulous There is little if any change in the distal portion of the extremities At times the changes in configuration of the patient take place without gain in weight The patients develop a plethoric and cyanotic hue suggestive of polycythemia which however

sat at home without interest or occupation She became mentally dull and introspective Her appearance assumed the characteristics of Cushing s syndrome She presented also the usual laboratory and x ray findings In the course of a year following the removal of an adenoma of the right adrenal gland by Dr George I Cahill the physical characteristics of her disease disappeared and she had a complete change in personality (Fig 4) She became quite gregarious and returned to a full time gainful occupation Unfortunately, many of the adrenal cortical tumors which give rise to Cushing's syndrome, are malignant, and fatal recurrence often follows temporary alleviation of the syndrome

In the absence of demonstrable neoplasia and in patients in whom there is no obvious hyperplasia of the adrenal cortex two types of treatment may be employed Radiation of the pituitary or adrenal glands has been employed with some improvement in a number of patients It is possible that the benefit noted may have resulted from spontaneous remission in the disease process Albright recently has described striking improvement in a number of patients as a result of continued treatment with 25 mgm of testosterone or methyl testosterone daily In these patients Albright has reported increase in strength associated with the establishment of a positive nitrogen, phosphorus and calcium balance There has been an increase in deposition of calcium in the bones, the facial contours have reverted toward normal and the plethoric appearance has decreased In contrast to the salutary effects reported is the acceleration of growth of facial and body hair The ultimate results of this type of treatment are not yet established Most patients with Cushing's syndrome live less than ten years

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CHAPTER XIV

ENDOCRINE FUNCTIONS OF THE HYPOPHYSIS

By HARRY B FRIEDGOOD

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PART I

ANATOMY EMBRYOLOGY AND PHYLOGENY OF THE HYPOPHYSIS CEREBRI

INTRODUCTORY REMARKS

An adequate conception of the clinical and functional pathology of the hypophysis cannot be achieved other than through precise information concerning the morphological structure and anatomical relations of the constituent parts of this endocrine organ A systematic nomenclature which is based on functional as well as morphological considerations, is a very important aspect of this view point

There was a time during the development of notions concerning hypophysial structure when anatomists and clinicians alike referred to the anterior and posterior lobes of the hypophysis with apparent morphological and functional specificity Neither this terminology nor the viewpoint which fostered it appears to be tenable any longer Numerous studies especially those of Tilney have introduced a more significant conception of the morphology and therefore of the physiology and pharmacology of the hypophysis These topographical observations have disclosed that the so-called anterior and posterior lobes are each composed of several subdivisions which are neither in the anterior nor posterior position respectively In the literature the term anterior lobe refers quite generally to the pars distalis of the adenohypophysis whereas the designation posterior lobe is equivalent to the processus infundibuli of the neurohypophysis

The subdivisions of the adenohypophysis include the pars distalis pars intermedia pars infundibularis and the pars tuberalis and the neurohypophysis has been subdivided into the processus infundibuli pediculus infundibularis bulbus infundibularis and labrum infundibularis or median eminence of the tuber cinereum (Fig 1) With the exception of certain neurophysiologists who have been concerned with the experimental study of this region relatively recently few investigators have paid much attention to the functional importance of these subdivisions Most physiological and pharmacological experiments have been aimed either at the 'anterior" or posterior lobe Perhaps a majority of the conflicting and mutually incompatible observations which are recorded in the literature can be attributed to this misconception

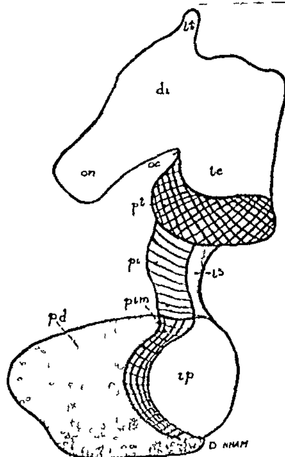


FIG 1 Reconstruction of hypophysial region in an adult female 61 years old Reconstruction illustrates the critical changes in the angulation of hypophysial axis This angulation now is approximately 90° with the floor of the third ventricle Specimen No 1184 di diencephalon ip infundibular process is infundibular stem le lateral eminence of tuber cinereum lt lamina terminalis oc optic chiasm on optic nerve pd pars distalis pi pars infundibularis pim pars intermedia pt pars tuberalis After Tilney with modification by Rasmussen

To avoid this dilemma the physiologist must know precisely what anatomical structures he has stimulated or destroyed experimentally How else can one correlate the experimental pathology with the resultant disordered physiology? For instance it is virtually impossible to puncture the preinfundibular area of the tuber cinereum without damaging and destroying portions of the adenohypophysial pars tuberalis The functional disorders, which are observed postopera

tively in such cases have been attributed almost universally to the hypothalamic damage alone Moreover observations on the pharmacological and physiological activity of extracts of the various divisions of the hypophysis cerebri presuppose an exact knowledge of the anatomical source of the crude material Failure to appreciate this viewpoint and to put it into practice cannot result in other than the misinterpretation of data and the improper anatomical localization of function A classical example of this type is to be found in the case of the pars infundibularis of the adenohypophysis It is a relatively large structure, which is closely adherent to and at some points merges with the pediculus infundibularis of the neurohypophysis It has been ignored for the most part in physiological and pharmacological experiments which have been aimed solely at the neurohypophysis Most pharmacological preparations of the so called posterior lobe' of the ox pig or sheep contain the anatomically conspicuous parenchyma of the pars infundibularis of the adenohypophysis but this factor has not been taken into account either at the bedside or in the laboratory

Allied to these problems and of equal importance is an understanding of the functional significance of the normal cytology of the hypophysis cerebri and of the cytological changes which characterize certain physiological states of the organism A useful clinical conception of the manner in which various hypophysial endocrinopathies are interrelated depends in large measure on information of this type

Finally a proper perspective of the morphological biological and clinical significance of the hypophysis must include some knowledge of its embryological development and its relation to the whole system of cerebral glands of which it is only a part albeit the most important in man

This chapter has been written with the foregoing considerations in mind and the incorporated clinical and experimental data have been discussed from this viewpoint whenever the opportunity has presented itself

Clinical Aspects of the Anatomy and Embryology of the Hypophysis Cerebri

General Appearance and Topography

The hypophysis cerebri is an ovoid reddish gray mass the diameters of which measure about 7 to 10 mm anteroposteriorly 10 to 15 mm transversely and 4 to 7 mm vertically As these measurements indicate the largest diameter of the gland lies in a frontal plane

The hypophysis occupies the fossa hypophyseos in the sella turcica of the sphenoid bone where it is roofed in by the diaphragma sellae The latter is fused

with the upper surface of the body of the gland The shape and differentiation of the hypophysial fossa varies considerably within certain limits The depth is the most variable of its three dimensions This circumstance has an important clinical bearing A growing hypophysial tumor can expand readily in all directions, when the fossa is shallow the anterior wall almost absent and the dorsum sellae poorly differentiated On the other hand, an expanding hypophysial tumor would be directed upward and forward when the anterior wall of the fossa is relatively low In such cases the dorsum sellae with its posterior clinoid processes is elongated and bent forward not infrequently More commonly, however, enlarging tumors of the hypophysis project backward and erode the dorsum sellae and its posterior clinoid processes Schaeffer[3] suggests that the course of direction of the infundibulum may be a factor in determining the direction of growth of a hypophysial tumor inasmuch as the majority of infundibula extend posteriorly and superiorly In this connection it is well to recall that the dorsum sellae is extremely variable in its differentiation and anatomy, and that the posterior clinoid processes may be absent congenitally Furthermore, deformation of the outlines of the sella with erosion of the posterior clinoids is by no means pathognomonic of a local lesion, because cerebellar tumors have been known to give an identical roentgen picture Hence the roentgen interpretation of alterations in the bony anatomy of the dorsum sellae must be made with caution

On either side of the sella turcica is the approximately longitudinal bony channel which contains the cavernous sinus These sinuses which drain the ophthalmic vein and its smaller tributaries also contain the post ganglionic nerves of the superior cervical sympathetic ganglia which reach them via the carotid plexus and four cranial nerves the third fourth sixth and ophthalmic division of the fifth The third cranial nerves pass forward through a lateral notch in the posterior clinoid processes and thus are particularly vulnerable to pressure from an enlarged hypophysis The relations of the hypophysis to the structures superior and anterior to it likewise are of special clinical importance Schaeffer[3] believes that the generally accepted views on this point are essentially inaccurate It is stated commonly that the chiasm lies in the optic groove of the sphenoid bone with the hypophysis and infundibulum posterior to the optic chiasm In a study of freshly exposed brains (Fig 2) Schaeffer found that this holds true for only 5 per cent of the cases (Fig 2 A) In 95 per cent of the cases the optic chiasm is located wholly or partly over the diaphragma sellae and the underlying hypophysis In 79 per cent of his preparations the hypophysis was found completely anterior and inferior to the chiasm and protruded somewhat laterally beyond the chiasm (Fig 2 C) In 12 per cent of the cases the chiasm itself lay markedly posterior to the optic groove while the body of the hypophysis was located directly beneath the chiasm (Fig B) When viewed from above por

tions of these hypophyses were visible anterior as well as posterior to the chiasm In 4 per cent of Schaeffer s cases the entire mass of the hypophysis was located anterior to the chiasm with no visible protrusion laterally (Fig 1 D) In such cases the entire optic chiasm is located behind the sellar diaphragm in such a fashion that it rests upon the dorsum sellae and partially projects behind it

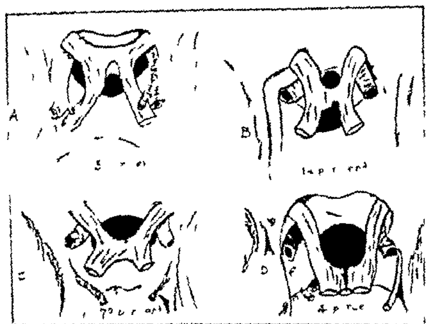


Fig 1 Showing varieties of relations of the optic chiasm internal carotid arteries and hypophysis After J Parsons Schaeffer

A The usually presented type but actually existing in only 5 per cent of the cases The chiasm in the optic groove B The pituitary underlying the chiasm both anteriorly and posteriorly The chiasm markedly posterior to the optic groove (12 per cent) *C The hypophysis completely anterior and inferior to the chiasm and protruding laterally beyond the chiasm* The most frequent finding (9 per cent) *D* The entire mass of the hypophysis anterior to the chiasm with no lateral protrusion (4 per cent)

In order to reach its postchiasmal position the infundibular process must in most cases pass along the base of the chiasm anteroposteriorly in a saggital plane *Thus it practically comes into direct contact with the chiasm and occasionally* even indents its inferior aspect These anatomical relations indicate how readily an enlarging hypophysial gland can affect one or both aspects of the chiasm pro*ducing either a homonymous hemianopsia on the side contralateral to the pressure*

or a bilateral hemianopsia depending on whether the lesion expands unilaterally or symmetrically These anatomical findings explain also how the disordered physical relations of an enlarged hypophysis could be transmitted along the course of the infundibulum and result in pressure and traction on the chiasm

The dorsum sellae and the posterior clinoid processes make up the posterior aspects of the hypophysis This wall is thin and poorly calcified as a general rule and occasionally it is found that an expanding hypophysial tumor which erodes the partition even exerts pressure on the posterior hypothalamic region and the crura cerebri The physical relations of the hypophysis and optic chiasm are such therefore that an expanding lesion in the sella turcica may account for a complex group of subjective and objective symptoms and signs which include visual field defects hemicrania and other types of headaches circulatory disorders within the ocular orbit and pressure effects on the crura cerebri with the attendant contralateral motor and sensory symptoms

Major Divisions and Subdivisions

The major divisions and subdivisions of the hypophysis cerebri, which are tabulated in Table I have been classified on a morphological basis from a functional viewpoint This classification has particular merit, moreover, because it conforms in all important respects with what is known of the embryology of the hypophysis In general the classification is that of Tilney[1] as adopted and modified by Rasmussen[4] The terminology which has been employed is in accord with the recommendations of the International Commission on Anatomical Nomenclature (see Fig 1)

TABLE I

Divisions of the Mammalian Hypophysis

Major Divisions		Subdivisions
Adenohypophysis	Lobus glandulari	1 Pars distalis
		Pars intermedia
		3 Pars infundibularis
		4 Pars tuberalis
Neurohypophysis	Lobus nervosus	Processus infundibuli
	Infundibulum	1 Pediculus infundibularis (stem)
		2 Bulbus infundibularis (bulb)
		3 Labrum infundibularis (rim) or median eminence of the tuber cinereum

The adenohypophysis is distinguished from the neurohypophysis primarily on the basis of their embryological origins The adenohypophysis which is derived from the somatic ectoderm consists of the pars distalis pars intermedia,

pars infundibularis and pars tuberalis The structural pattern of the adenohypophysis as a whole and the anatomical interrelations of its four constituent parts are determined by their origin and subsequent developmental growth It will be recalled that a marked evagination Rathke s pouch, takes place from the roof of the mouth early in the embryological development of the hypophysis (Fig 3) The epithelium of the stomodeum and the floor of the diencephalon are in contact

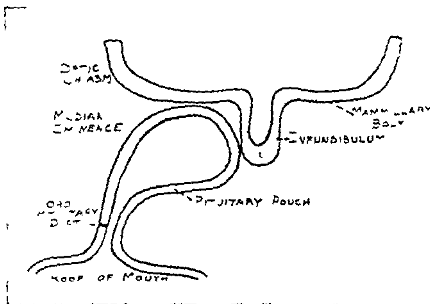
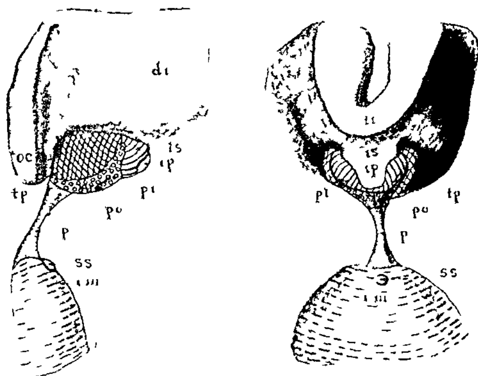


Fig 3 Sketch showing early relations of the pituitary pouch to the floor of the third ventricle particularly to the infundibulum After Tilney

and perhaps adherent to each other at this time Somewhat later there develops a protrusion downward from the floor of the ventricle This protrusion occupies a position which is immediately behind Rathke s pouch In the meantime a growth of mesenchymal tissue which invades the region between the floor of the brain and the roof of the mouth brings about a considerable separation of the oral cavity from the brain The connection between Rathke s pouch and the oral cavity lengthens gradually to form the long slender, oro hypophysial duct which eventually becomes solid and is known as the hypophysial stalk The ventral part of this stomodeal diverticulum becomes divided into two lateral lobes and a larger anterior portion in the 10 5 mm human embryo The anterior portion develops into the pars distalis of the adenohypophysis The pars tuberalis is derived from the bilateral extensions the tuberal processes of Rathke s pouch

which begin to fuse across the midline in the 45 mm embryo and eventually form a complete investment of the median eminence in the adult of the higher vertebrates

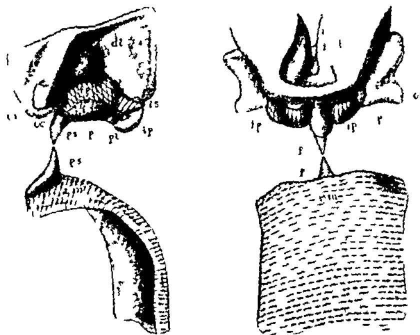
At about the same time two well defined changes occur in the dorsal or superior wall of Rathke s pouch, which is in contact with the neural protrusion from the



FIGS 4 AND 5 Left lateral and caudal views of reconstruction of hypophysial region in 16 mm human embryo Specimen No 1024 di diencephalon ip infundibular process is infundibular stem oc optic chiasm pi pars infundibularis po pituitary pouch ps pituitary stalk rm roof of mouth ss Seessel s pocket tp tuberal process After Tilney

entricle This juxtaneural epithelial region becomes thickened considerably and two caudal prolongations from it extend backward and almost surround the neural protrusion This thickened area together with its two caudal prolongations form the pars intermedia and pars infundibularis Tilney[1] prefers to regard this entire structure as the pars infundibularis On account of the long infundibular stem in the human hypophysis Rasmussen[4] has suggested, however, that the glandular parenchyma along the infundibular stem should be designated the

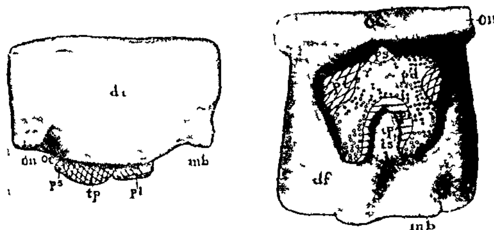
pars infundibularis, whereas the term pars intermedia should be reserved for glandular tissue which lies between the pars distalis and the processus infundibuli The extent to which the various portions of the adenohypophysis surround the infundibular stem in the adult is variable The pars infundibularis of the adenohypophysis may surround the infundibular stem completely as it emerges



Figs 6 and 7 Left lateral and caudal views of hypophysial region in 4 mm human embryo Specimen No 2010 di diencephalon ip infundibular process is infundibular stem oc optic chiasm on optic nerve pi pars infundibularis po pituitary pouch ps pituitary stalk rm roof of mouth tp tuberal process After Tilney

from the processus infundibuli The pars infundibularis and its continuation the pars tuberalis extend upward and become increasingly more posterior until they cover completely the posterior aspect of the infundibular bulb and the median *eminence of the tuber cinereum The amount of glandular epithelium is variable* and may become very scanty in the region of the upper portion of the infundibular stem and the tuber cinereum where there are numerous large vascular channels according to Wislocki[547]

As the anterior portion of Rathke s pouch grows larger, it is differentiated into an irregular highly vascularized network of cells which constitute the pars distalis of the adenohypophysis The residual lumen of Rathke s pouch, which persists in most mammals and in the lower vertebrates, serves to separate the pars distalis from the pars intermedia and processus infundibuli The pars intermedia is considered by some authorities[8] to be the most ancient part of the hypophysis It



Figs 8 and 9 Left lateral and basal views of reconstruction of hypophysial region in a 30 mm human embryo Specimen No 2040 df diencephalic floor di diencephalon i infundibulum ip infundibular process is infundibular stem mb mammillary body oc optic chiasm on optic nerve pd pars distalis pi pars infundibularis ps pituitary stalk pt pars tuberalis tp tuberal process After Tilney

forms an investment of the processus infundibuli and usually is confined in its neural contact to the hypophysial surface of this process The pars distalis is separated distinctly from the floor of the brain by a fairly thick layer of connective tissue as far back in its phylogenetic history as the cyclostomes Its relation to the cerebrum thus is far less intimate than that of the pars infundibularis or the pars tuberalis It is not surprising therefore to find that in the higher vertebrates, including reptiles birds and mammals the pars distalis becomes progressively more distant from the floor of the third ventricle This glandular tissue of the pars distalis consists of two distinctly different regions the cortex and medulla each of which has distinguishing cytological characteristics which will be described in detail in another connection The histological differences between the two portions of the pars distalis are distinct The cortical zone takes a relatively light stain which discloses principally basophiles among which are scattered numerous chromophobes and its large acini are embedded in extensive interacinal cell

masses. The medullary zone consists of smaller, more compact acini; its interacinal cell masses are more limited and its deeply staining cells are largely acidophilic[1].

The infundibular region, towards which Rathke's pouch is attracted, is by no means passive in the matter of biotaxis, although as a general rule it is the somatic ectodermal anlage of the hypophysis which manifests the most pronounced growth. The intimate interrelations between the buccal and neural ectodermal origins of the hypophysis and the dependence of each upon the other for normal growth are evidenced by failure of the somatic portion to develop if contact with



FIGS. 10 AND 11. Lateral and caudal views of reconstruction of hypophysial region in a 5 months human fetus. This stage shows the early effect produced by the lengthening of the infundibular stem and process. The pars tuberalis is now completely exposed on the base of the brain as it invests the median eminence of the tuber cinereum. Specimen 2022. df, diencephalic floor; dl, diencephalon; ip, infundibular process; le, lateral eminence; ml, mammillary body; oc, optic chiasm; on, optic nerve; pd, pars distalis; pi, pars infundibularis; pr, preoptic recess; pt, pars tuberalis; e, saccular eminence. After Tilney.

the floor of the brain is interfered with experimentally[1] and by retardation in growth or abnormal development of the neurohypophysis if experimental ablation of the adenohypophysis is carried out early enough[2]. In some species the infundibular region shows extremely active expansion and in all vertebrates it furnishes the central point of attraction towards which Rathke's pouch is directed and by which its growth is limited. The infundibular region appears to have the most definite power of attraction in this phenomenon of biotaxis, but the entire floor of the ventricle from the caudal fibers of the optic chiasm to the mammillary bodies is believed to exert a certain degree of attraction. That the floor of the third ventricle other than the infundibular region exerts attraction for the glandular epithelium of Rathke's pouch is shown by the constant relations of the lateral processes or tuberal sprouts to the median eminence.

The portion of the brain which contributes to the origin of the hypophysis

includes an area in the floor of the third ventricle extending from the caudal fibers of the optic chiasm to the mammillary bodies (Figs. 10 and 11). The earliest parts derived from the neural ectoderm consist of the median eminence of the tuber cinereum and the infundibulum. The median eminence represents a protuberance from the floor of the third ventricle which begins to take form immediately caudal to the optic chiasm and extends backward as far as the cephalic limits of the premammillary area. The median eminence is characterized by a more pronounced degree of bulging in man and apes as compared with other mammals, possibly because there is a greater descent of certain parts of the hypophysis into the deepened sella turcica of the primates. The median eminence is flanked by the lateral eminences of the tuber cinereum. In early embryonic stages the infundibulum is a funnel-shaped process evaginating from the floor of the third ventricle just posterior to the area occupied by the median eminence. The infundibulum is characterized embryologically by a ventral surface, which is in contact with the pouch destined to become the adenohypophysis, and a dorsal surface which gives rise to a structure known as the saccus vasculosus[1]. The relative position of the ventral and dorsal surfaces of the infundibulum, which varies from species to species, determines the regional topography of the fully developed neurohypophysis. The saccus vasculosus has the characteristic histological architecture of a secreting glandular tissue in all species. This has been determined by the structure of the epithelial cells as well as by the vascularity of this region. Moreover phylogenetic studies, particularly in reptiles, birds and certain mammals, e.g. the cat, indicate that the saccus vasculosus is an integral part of the infundibulum and consequently of the neurohypophysis[1]. This may be of considerable physiological significance. Accepting Tilney's embryological observations at face value, they imply that the so-called "posterior lobe" or processus infundibuli contains glandular inclusions derived from the saccus vasculosus. It might be offered as a guarded suggestion that the nests of epithelial cells which occur as isolated clusters scattered throughout the dorsal portion of the processus infundibuli of the dog represent glandular inclusions derived from the saccus vasculosus.

The infundibulum is a tapering extension from the ventral surface of the median eminence and contains a central cavity which is continuous with the third ventricle. Its cavity is retained in the cat but disappears in man. The infundibulum projects backward and downward from the caudal extremity of the median eminence in most mammals below the primates, but in man the line of its projection is directly downward because of the descent of the hypophysis into the deepened sella turcica. The infundibular structure consists of the bulb which marks its attachment to the floor of the third ventricle and the stem which connects the bulb with the infundibular process. The latter is more commonly

known as the "posterior lobe." In man the infundibular stem is a solid stalk of considerable length which passes through an opening in the diaphragma sellae to terminate in the dependent part of the hypophysis known as the processus infundibuli.

The four neural structures which have just been described are known as the labrum infundibularis or median eminence of the tuber cinereum, the bulbus infundibularis or infundibular bulb, the pediculus infundibularis or infundibular stem and the processus infundibuli or lobus nervosus. They constitute the neurohypophysis and must be considered as a functional unit from a physiological and clinical viewpoint. They contain at least two nerve fiber systems, the supra-optico-hypothalamic and tubero-hypothalamic tracts, which extend from the hypothalamus through the stem and end in the processus infundibuli. They will be described in detail in Part V and in the chapter on the hypothalamus.

Because of the embryological and anatomical data which have been presented above, it seems clear that the terms "anterior lobe" and "posterior lobe" are inadequate either from a physiological or a morphological viewpoint. As a corollary one must conclude, furthermore, that the interests of the clinician and the pathologist are served best by the adoption of the nomenclature and conception fostered by Tilney and others of his way of thinking.

The Craniopharyngeal Duct and Canal

Anlage and Incidence. — In order to emphasize the functional as well as the morphological aspects of the foregoing classification, certain special phases of the developmental history of the hypophysis cerebri are recorded herewith. Such an approach serves to clarify the clinical significance of certain embryological rests in the hypophysial area. The relation of these vestigial remnants to the origin of tumors which are peculiar to this region is an important part of this problem.

Rathke's original conclusion that the hypophysis cerebri has a two-fold anlage is accepted almost universally now. Most investigators, including Tilney, Kolliker, Dohrn, Froriep[13], Scott, Balfour, Emery, and Mirot, have upheld Rathke's belief that the hypophysis arises from two specialized sources of ectoderm, the somatic ectoderm in or about the region of the roof of the mouth and the neural ectoderm in the floor of the third ventricle. This interpretation of the available embryological data has been challenged by Hoffman, Kupffer, Valenti, Prather, Bruni, and Balfour and Parker on the basis of their studies of bony fish, amphibia and reptiles. Their observations have disclosed what they take to be an entodermal participation in the formation of the hypophysis. In view of this evidence one must conclude that the entoderm does participate in the formation of the gland in some lower vertebrates, but there is no reason as yet to

includes an area in the floor of the third ventricle extending from the caudal fibers of the optic chiasm to the mammillary bodies (Figs 10 and 11) The earliest parts derived from the neural ectoderm consist of the median eminence of the tuber cinereum and the infundibulum The median eminence represents a protuberance from the floor of the third ventricle, which begins to take form immediately caudal to the optic chiasm and extends backward as far as the cephalic limits of the premammillary area The median eminence is characterized by a more pronounced degree of bulging in man and apes as compared with other mammals possibly because there is a greater descent of certain parts of the hypophysis into the deepened sella turcica of the primates The median eminence is flanked by the lateral eminences of the tuber cinereum In early embryonic stages the infundibulum is a funnel shaped process evaginating from the floor of the third ventricle just posterior to the area occupied by the median eminence The infundibulum is characterized embryologically by a ventral surface, which is in contact with the pouch destined to become the adenohypophysis and a dorsal surface, which gives rise to a structure known as the saccus vasculosus[1] The relative position of the ventral and dorsal surfaces of the infundibulum which varies from species to species determines the regional topography of the fully developed neurohypophysis The saccus vasculosus has the characteristic histological architecture of a secreting glandular tissue in all species This has been determined by the structure of the epithelial cells as well as by the vascularity of this region Moreover phylogenetic studies particularly in reptiles birds and certain mammals e g the cat indicate that the saccus vasculosus is an integral part of the infundibulum and consequently of the neurohypophysis[1] This may be of considerable physiological significance Accepting Tilney's embryological observations at face value they imply that the so called "posterior lobe" or processus infundibuli contains glandular inclusions derived from the saccus vasculosus It might be offered as a guarded suggestion that the nests of epithelial cells which occur as isolated clusters scattered throughout the dorsal portion of the processus infundibuli of the dog represent glandular inclusions derived from the saccus vasculosus

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marks the position of the so called craniopharyngeal canal Tilney[1] could not be certain whether this canal was patent but concluded that it did not contain remnants of the hypophysial stalk in any event

There are certain clinical aspects to the so called craniopharyngeal canal which are pertinent to the discussion This structure was named in 1868 by Landzert[8] who found a complete canal passing through the body of the sphenoid bone in 10 per cent of newborn children and Le Double[9] in 1903 observed the same incidence under similar circumstances In view of more recent studies Cave[10] believes that they were confusing this canal with the relatively common vascular foramina of the sphenoidal body Tilney[1] states that it occurs in less than 0 5 per cent of presumably normal crania of all ages and Cave[7] concurs with an incidence of 0 2 per cent based on a study of adult human skulls Greig[1] has observed it in 40 per cent of anthropoid apes and has encountered it relatively frequently in other animals Tilney believes that it should be called the orocranial canal inasmuch as its ventral end originates primarily in relation with the roof of the mouth and only secondarily comes to occupy a position in the pharynx where it is situated 5 5 mm posterior to the nasal septum Reference to it as the craniopharyngeal canal implies erroneously that the hypophysis is derived from the pharynx Evidence of its vestigial remains may be disclosed occasionally by an opening in the floor of the sella turcica[9] Cave[0] recorded such a case in a 38 year old male The mouth of the craniopharyngeal or orocranial canal was a circular hole in the floor of the sella turcica 3 5 mm in diameter which could be entered by a probe for a distance of 16 mm downward and forward through the median septum of the sphenoidal sinus to a vomerine termination in the nasal septum Cases have been reported in which the canal is complete and contains a prolongation of dura which merges with the periosteum covering the undersurface of the sphenoid bone Other instances have been observed however in which the canal is incomplete contains a dural cul de sac with or without hypophysial tissue and terminates in the body of the sphenoid or in the posterior part of the nasal septum An example of this type where an incomplete canal was filled by a solid epithelial plug was observed in a 4 year old child by Suchannek[8] When the canal presents an inferior opening Cave states[3] that the aperture is located usually about 1 5 mm behind the postero superior angle of the vomer Frazier[7] points out similarly that the ventral extremity of the craniopharyngeal canal ends in or near the vomer bone Haberfeld[4] reviewed 73 cases of persistent craniopharyngeal or orocranial canal and concluded that the canal is more likely to be present if other malformations are found According to Goldzieher[15] the canal can be recognized on lateral roentgenograms of the skull

Clinical Significance of Vestigial Remnants — The Craniopharyngioma — Although divergent views are held concerning the possible fate of certain of the

implicate the entoderm in the embryological development of the hypophysis of the primates Tilney s summary[1] of the evidence indicates that entodermal cells of the foregut notochord or premandibulbar somites apparently do not enter into the formation of this organ these structures are contiguous to, but probably not con tinuous with, the germ layers which participate in the formation of the gland

There is some discussion over the nature of the forces that take part in the early approximation of the somatic and neural ectodermal tissues which contribute to the formation of the hypophysis Gilbert states, contrary to general belief, that the hypophysis is not formed from evaginations, which arise from their respec tive anlage and that the latter do not approach each other through biotaxis [6,7] Her observations indicate that the hypophysis develops at a point where the two ectodermal anlage are adherent long before either of the hypophysial diverticuli is recognizable and the manner in which the head region of the embryo develops, viz, the mechanical forces induced by the ventral bending of the forebrain apparently determine the formation and shape of Rathke s pouch More general acceptance has been accorded the theory, however which proposes that tubular diverticuli in the form of closed sacs grow out from the ectodermal anlage Having been attracted definitely to each other by virtue of biotaxis they meet to form the hypophysis According to this conception Rathke s pouch grows out dorsally from the ectoderm of the primitive buccal cavity its precise point of origin being subject to some variations in the various phyla (see Fig 3) Rathke's pouch communicates at first with the buccal cavity through a wide connection in the roof of the mouth Later this connection becomes elongated to form a slender tubular structure known as the *craniopharyngeal duct* The latter is a misnomer according to Tilney[1] because the duct takes origin from the roof of the mouth and not from the pharynx Tilney has suggested a more appropriate name the *oropituitary duct* In keeping with the nomenclature adopted for this chapter one might refer to it as the *orohypophysial duct* Subsequently, early in its de velopment the orohypophysial duct becomes a solid structure the hypophysial stalk which extends between the roof of the mouth and Rathke's pouch Coin cident with these changes the mesenchyme invades extensively the region between the floor of the brain and the roof of the mouth The mesenchymal foundations of the sphenoid bone are formed in this manner and the hypophysial stalk, which is surrounded by rapidly growing sphenoidal mesenchyme comes to occupy the so called *craniopharyngeal canal* The hypophysial stalk, which develops from the extremely transitory orohypophysial duct becomes attenuated and disappears in turn except for a small remnant which remains attached to the roof of the mouth while another remnant can be identified at the cephalic extremity of the hypophy sis According to Tilney[1] the sphenoidal anlage in the 30 mm human embryo is distinctly cartilaginous and contains a small circular area near its center, which

The tumors are of two types in general viz cystic or solid The cysts may be smooth, thin walled and unilocular or multilocular The solid tumor usually is firm and lobulated Mixed varieties of tumors are not infrequent There are solid squamous cell tumors containing intracystic papillomatous structures and others in which degeneration and cyst formation occur because of a blood supply which becomes inadequate as the tumor increases in size In such cases secondary calcification and ossification of the wall may serve as an important roentgenological diagnostic sign At operation such cystic tumors frequently are found to be filled with thick grumous fluid rich in cholesterol crystals of cholesterol may lie free in the fluid and are to be found also in the fibrous tissue wall The latter have been confused with meningeal cholesteatomata The solid tumors are of two kinds ordinarily, i e the epidermoid cell carcinoma of the squamous type and the basal cell carcinoma of the adamantinoma variety The epidermoid cells are of the usual structure with typical intercellular bridges and keratinization and the tumor tends to metastasize The basal cell type which usually invades adjacent structures but does not metastasize is characterized by a centrally placed enamel syncytium, within which are epidermoid pearls the horn pearl formation and a peripheral columnar enamel epithelium [9] Teratomas are rare in the vicinity of the sella turcica[4]

The symptoms and signs produced by the so-called craniopharyngiomas will be discussed in detail in relation to the pathogenesis of dwarfism For the present it is sufficient to state that they may elicit obesity hypersomnolence and polyuria by virtue of pressure upon or invasion of the hypothalamic region Pressure atrophy of the adenohypophysis in children results among other things in retarded somatic and gonadal growth loss of body hair and hypometabolism Failing libido impotence and amenorrhea develop in postpuberal individuals under similar circumstances It is pertinent to note in this connection that the hypothalamus may be involved in the production of certain symptoms which have been ascribed heretofore to adenohypophysial dysfunction alone The basis for this suggestion is being discussed at some length elsewhere in the chapter on the hypothalamus

Pharyngeal Hypophysis — The pharyngeal hypophysis is named incorrectly from an embryological viewpoint because the hypophysial structures of which it is a vestigial remnant take origin from the roof of the mouth and not from the pharynx According to Cave [9] the so-called pharyngeal hypophysis was observed originally by Killian in 1888 It was studied subsequently by Erdheim[25] Haberfeld [1] Cristeller[12] Gautier [2] Pende[4] and Melchionna and Moore[45] It is said to be present almost constantly in humans if carefully searched for Melchionna and Moore[45] observed it in 51 of the 54 cases they studied They found the pharyngeal hypophysis in the midline beneath or near the vomerosphenoidal

residual structures of the early buccal anlage, there is general agreement on the thesis that the craniopharyngioma type of tumor takes origin from these vestigial structures According to Tilney[1] there is no acceptable proof that any part of the orohypophysial duct is carried over into the adult state of man It should be recalled, however that one remnant of the orohypophysial duct remains attached to the roof of the mouth presumably becoming the so called *pharyngeal hypophysis* whereas another remnant has been observed at the cephalic extremity of the hypophysis Embryologically the latter becomes associated intimately with the developing pars tuberalis of the adenohypophysis This may be significant inasmuch as Atwell believes that tumors in this general area take origin from rests in the pars tuberalis Atwell s conception appeals to Tilney[1] because it explains satisfactorily the presence in this region of tumors of the adamantinoma structure The early intimate relation of the hypophysial plate to the dental ridge accounts for the inclusion of dental elements into the anlage of the pars tuberalis Tiney objects to Erdheim s postulation[3] that tumors of the so called craniopharyngioma type are derived from embryological rests along the course of the orohypophysial duct The importance of Erdheim s observations must be recognized even though Tilney may be correct concerning the complete disappearance of the orohypophysial duct early in the development of the embryo Erdheim was the first to ascribe the origin of the craniopharyngioma type of tumor to the anlage of the orohypophysial duct It should be recalled in this connection that the pars tuberalis is derived embryologically from paired structures which bud from the orohypophysial duct From an embryological viewpoint, therefore Atwell s theory is not far removed from that of Erdheim

As might be expected the so called craniopharyngioma usually is suprasellar due to its probable origin from embryonal squamous cell rests in the pars tuberalis of the adenohypophysis Occasionally however the tumor may develop within the sella turcica itself a finding which is compatible also with the embryological characteristics of this region The tumor may appear at any period of life but is especially common under fifteen years of age It attains a much larger size ordinarily than the average hypophysial adenoma Because of its usual suprasellar position it does not balloon out the sella turcica like the latter tumor but flattens it from above downward As a result of this pressure it destroys the diaphragma sellae and erodes the dorsum sellae at the same time that it produces pressure atrophy of the hypophysis cerebri The atrophy of this gland may be so complete that it is recognizable only microscopically These tumors also grow upward and encroach either by pressure or invasion upon the tuber cinereum and the wall of the third ventricle In some instances the cavity of the third ventricle itself is invaded and the circulation of the cerebrospinal fluid is interfered with so that marked hydrocephalus of the lateral ventricles develop

Weight of the Constituent Parts in Relation to Race Sex Age Body Measurements and Pregnancy

The human hypophysis varies greatly in weight under conditions which are well recognized for the most part The factors with which these significant variations have been correlated are race, sex, body height and weight, age and physiological states such as pregnancy

The average weight of the hypophysis of the negro is greater than that of white people[4] The female hypophysis is heavier on the average than that of the male in all races which have been studied[4] Rasmussen s studies[46 7] of 111 adult men with an average age of 45 years and 93 non pregnant females with an average age of 41 years disclosed that the hypophyses of the former ranged in weight from 358 to 788 mgm, average 526 mgm while those of the latter ranged in weight from 448 to 971 mgm, average 618 mgm The pars distalis which is larger in the female than in the male accounts for the difference in size The processus infundibuli and pars intermedia on the other hand are significantly larger in the male Since the body weight of the female is less than that of the male ordinarily the proportional size of the female hypophysis exceeds the male gland even more than does its actual size Rasmussen has demonstrated also that there is a sex difference in the tendency for the outgrowth of tubular glands from the pars intermedia into the processus infundibuli inasmuch as such glands are noted more commonly in females than in males[48] There is a statistically significant positive correlation between body length or height and the weight of the hypophysis[4 49 50] The existence of a correlation between body weight and hypophysial weight has not yet been established with certainty[50 51 52] There is no correlation between the percentage of acidophilic cells in the hypophysis and stature although these cells are believed to be the source of the growth hormone[4]

The pars distalis of the male hypophysis decreases significantly in weight after middle age whereas the processus infundibuli and the epithelial elements of the pars intermedia tend to increase with age[4] In the female age changes are not reflected clearly in the weight of the whole gland a they are in the male Pars distalis retains its weight better than in males and the processus infundibuli and pars intermedia increase distinctly The growth of pars intermedia with age is due to an increase in basophilic cells which tend to invade the processus infundibuli[4]

The hypophysis becomes markedly enlarged during pregnancy[4 53] The amount of enlargement depends on the duration of pregnancy the length of time intervening between parturition and death and apparently also on the number of previous pregnancies Rasmussen s data indicate that the average weight of hypophyses of 8 primipara is 820 mgm whereas the corresponding figure for a

articulation deep in the mucosa or in the periosteum It occurs most frequently in the shape of a single flattened spheroid which is well circumscribed and encapsulated In a few instances irregular cords or islands of cells extend into the surrounding tissue

The largest pharyngeal hypophysis noted by Melchionna and Moore[45] was in a 15 year old girl and it measured 6 67 mm in length, 1 15 mm in width and 0 55 mm in depth The smallest gland they encountered was in a newborn infant and its dimensions were 0 22 mm in length, 0 21 mm in width and 0 10 mm in depth In a study of 51 cases Haberfeld[11] found that most of the growth of this gland occurred in the fetus during the first few months of life and that there was little or no enlargement thereafter This has been confirmed by Melchionna and Moore[45]

Studies of the histology of the pharyngeal hypophysis have disclosed essentially two types of tissue viz undifferentiated epithelial cells and differentiated cells similar to those of the adenohypophysis Melchionna and Moore[45] have reported that the undifferentiated epithelium was present in 32 of their 51 cases It is usually of the transitional type but in rare instances there may be definite intercellular bridges Keratinization and keratin granules do not occur The undifferentiated cells are arranged in small nests with an indefinite basal layer Cyst formation within the transitional epithelium occurs infrequently Not uncommonly there are glandular acini which are lined by columnar or cuboidal cells and associated with nests of transitional epithelium The acini contain a homogeneous acidophilic substance The differentiated tissue has the same histological appearance as that of the adenohypophysis but there are conspicuous quantitative differences between them The pharyngeal hypophysis shows a striking deficiency of basophilic and acidophilic cells They constitute less than 1 per cent of all cells In 25 per cent of the cases reported by Melchionna and Moore there were no chromophilic cells and in 35 per cent either the acidophilic or the basophilic cells were absent Fuchsinophilic colloid was associated frequently with the chromophilic cells and was conspicuous in 11 of their cases

The interstitial tissue and vascular supply of the pharyngeal hypophysis is essentially the same as that of the adenohypophysis There are numerous myelinated nerves and large vascular sinusoids in the tissue surrounding the pharyngeal hypophysis in most cases

Melchionna and Moore[45] have concluded that the pharyngeal hypophysis is not physiologically active in normal states of growth and metabolism Although the pharyngeal hypophysis does not appear to develop compensatory changes or hypertrophy when adenohypophysial function is disordered, there are some histological data which suggest that it is functionally active under certain circumstances[48]

and is far less intense than the corresponding physiological state in the female It should be recalled in this connection that the increased percentage of basophiles in the hypophysis of the menopausal woman occurs coincidentally with the increased urinary excretion of follicle stimulating hormone FSH This evidence of physiological hyperactivity of the pars distalis which is encountered commonly in the climacteric female occurs relatively infrequently in the middle aged male

The correlation between body length and the weight of the hypophysis also appears to have clinical significance and will be considered more fully in connection with the cytology of the pars distalis The increase in weight of the hypophysis during pregnancy may be of especial clinical importance because it probably contributes to the development of certain pathological states such as acromegaly hyperthyroidism and diabetes mellitus which complicates pregnancy sometimes This matter will be discussed further in connection with the cytophysiology of the adenohypophysis

Meningeal Relations

The meningeal relations of the hypophysis cerebri (Fig 12) are of clinical importance for at least two reasons In the first place the manner in which the meninges develop embryologically determines the mode and distribution of vascularization of the constituent parts of the hypophysis Consequently these data may have a specific bearing on the problem concerned with pathways of hormonal secretion The latter will be considered in connection with a description of the nerve and blood supply of the hypophysis Secondly the anatomical relations of the diaphragma sellae and the hypophysis throw considerable light on the direction in which a growing sellar tumor may expand

As a result of the studies of Schwartz and of Wislocki [6] it has been determined that neither the subarachnoid space nor the subdural space surround the hypophysis within the sella turcica The capsule of the body of the hypophysis, the dura lining the ella turcica and the periosteum covering the sph roid bone are intimately fused (Fig 12) This anomaly occurs because the dura becomes attached firmly to the body of the hypophysis before the meninges in this region are differentiated completely thus precluding the formation of a subarachnoid or subdural space within the sella turcica Early in its embryological development the hypophysis having been completely cut off from its oral origin comes to lie in a field of mesenchyme before the latter has undergone differentiation into meninges Subsequently the mesenchyme surrounding the body of the hypophysis gives rise to a lamina of dura which encloses the gland firmly and becomes attached to a portion of its upper surface leading to the formation of the diaphragma sellae

group of 46 multipara with a similar duration of pregnancy is 954 mgm If one limits such observations to multipara, who reached about full term and died within one week after parturition instead of up to two weeks as in the preceding groups the average hypophysial weight in 22 cases is 1,070 mgm A review of Rasmussen s data shows furthermore, that the difference in weight between the hypophyses of non pregnant and pregnant women is due entirely to an increase in the size of the pars distalis and amounts to well over 100 mgm Pars intermedia is smaller, if anything in the group of pregnant women

The physiological and consequently the clinical, significance of these variabilities in hypophysial weight have not been established with certainty There are too little data on differences which apply to racial groups, and this would seem to be a lucrative field of investigation for the geneticist and for those interested in the constitutional aspects of endocrine physiology So far as the physiology of the hypophysis is concerned the outstanding difference between the male and female gland is in its gonadotropic activities The occurrence of ovulation in connection with the menstrual rhythm and the phenomena of pregnancy parturition and lactation obviously require a highly complex physiological integration with other endocrine glands and body tissues Furthermore these unique female functions as compared with the physiology of the male sex hormone, call for a far greater precision in the homeostatic mechanisms which regulate organ and tissue metabolism That the acidophilic cells of the hypophysis play an important role in these anatomical and physiological differences is suggested by the fact that they are significantly more numerous in females than in males This conception is in accord with the data of Friedgood and Dawson [4 55 56], who noted a striking increase in the number of carmine cells during ovulation, parturition and lactation in rabbits and cats The carmine cell represents a functional variety of the ordinary acidophile

As noted above, the weight of the hypophysis as a whole and of the pars distalis in particular changes little after middle age in the female whereas it decreases significantly in the male This regression in hypophysial weight which occurs after physiological castration in the climacteric state is associated with a decrease in the percentage of acidophiles, an increase in the population of chromophobes and no significant numerical changes in the basophiles[4] On the other hand the relatively unchanged hypophysial weight in menopausal women is associated with a perceptible increase in the percentage of basophiles[4], while the percentages of acidophiles and chromophobes shift as in the male These findings may supply an anatomical and cytological basis to account for the clinical differences between the menopausal state of the male and female The regression in weight of the pars distalis and the lack of increase in the percentage of basophiles may explain why the male climacteric syndrome occurs much more infrequently

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The meningeal relations of the processus infundibuli likewise are noteworthy A mass of mesenchyme intervenes between the developing adenohypophysis and the base of the diencephalon to which it becomes attached by a slight condensation of cells forming pia mater The connective tissue stroma of the buccal hypophysis develops from this pial hypophysial mesenchyme by a gradual process

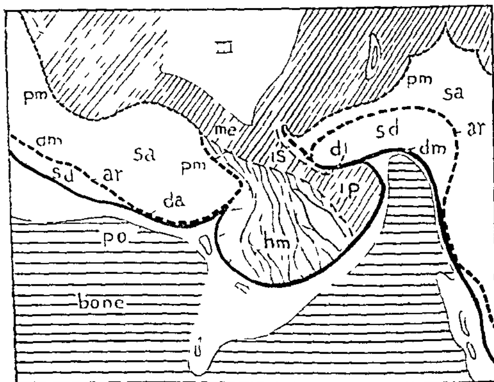


FIG 12 Diagram of the meninges in the hypophysial region of a human fetus of 160 mm Solid line dura mater (dm) Heavy interrupted line arachnoid membrane (ar) Light interrupted line pia mater (pm) It will be noted that the subarachnoid space (sa) forms a collar around the infundibular stalk (is) The pia arachnoid does not penetrate the sella instead the body of the pituitary is surrounded by dura (dm) which is fused with the free pole of the infundibular process (ip) and forms the sellar diaphragm (di) upon the upper surface of the body of the pituitary

At the margin of the pars tuberalis which extends forward beneath the median eminence (me) of the tuber cinereum pia mater (pm) and arachnoid (ar) meet In consequence the free surface of the pars tuberalis facing the subarachnoid space is covered by arachnoid

The pia mater (pm) is indicated by an interrupted line between the neurohypophysis and the buccal hypophysis Furthermore this lamina of pia is connected with a series of lines representing connective tissue stroma which subdivides the epithelial hypophysis The origin of the stroma (hm) from the pial hypophysial mesenchyma of earlier stages is indicated diagrammatically in this manner After Wislocki

of interdigitation of mesenchymal cells and hypophysial parenchyma The delicate condensation of cells which occurs on the surface of the diencephalon surrounds the entire neurohypophysis at first Soon however the infundibular process pushes its way into the mesenchyme of the developing fossa in the sella turcica As a result it loses any distinctive pial covering which it may have had and fuses with the dura within the sella The free pole of the infundibular process thus becomes attached to the dura When completely differentiated the subarachnoid space and the subdural space form a cistern which encloses the infundibular stem in the form of a collar The sellar diaphragm which is fused with the upper surface of the body of the hypophysis intervenes between the subarachnoid and subdural spaces on the one hand and the sella turcica on the other

The diaphragma sellae is a small more or less oval layer of connective tissue which roofs the hypophysial fossa in the horizontal plane The foramen of the diaphragma sellae is an extremely variable opening through which the infundibular stem emerges from the sella turcica The diaphragm is composed of fibro elastic tissue which varies from a very dense strong structure with a very small foramen to one which is frail largely absent and pierced by a relatively large infundibular foramen In some cases the greater portion of the diaphragm may be more or less fenestrated and of delicate structure

The anatomy of the diaphragma sellae may influence the direction of growth of a hypophysial tumor at times A tumor can expand readily toward the optic chiasm when the diaphragm is essentially absent or poorly developed On the other hand such tumors are more likely to expand in the direction of the sphenoidal sinuses if the latter are highly pneumatized and the diaphragm is exceptionally tough and complete A large opening in the diaphragm often delays recognition of an intrasellar tumor since it obviates the early headaches associated with expanding intrasellar neoplasms In such cases decompression occurs through the enlarged infundibular foramen

Blood Vessels and Lymphatics

Arteries and Veins in the Mature Human Hypophysis —The vascular supply of the hypophysis cerebri (Fig 13) has been studied minutely by Wislocki and others[62, 65, 60] It has been determined that the blood supply of the human hypophysis coincides with that of the rhesus monkey[61] The main arterial channels consist of the superior and inferior hypophysial arteries[67] The superior hypophysial arteries are derived from the internal carotids and the posterior communicating arteries These vessels are distributed to the infundibulum and the adenohypophysis The twigs entering the adenohypophysis break up into sinus

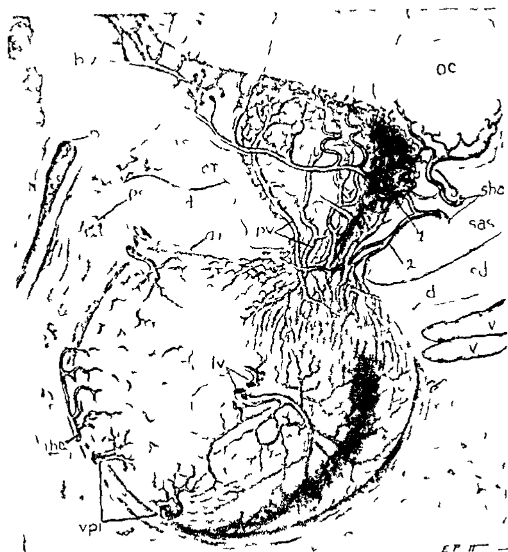


FIG 13 Schematic drawing of the hypophysis of the adult rhesus monkey ar arachnoid membrane ba basilar artery bv basilar veins d dura dl sellar diaphragm iha inferior hypophysial artery lv lateral hypophysial veins oc optic chiasm pc posterior clinoid process pv portal venules sas subarachnoid space sd subdural space sha superior hypophysial arteries (1 branches to hypophysial stalk 2 branches to anterior lobe) v dural vein vpi veins of infundibular process After Wislocki

oids Those vessels which supply the infundibulum enter a plexus of capillaries of sinusoidal character which surrounds and penetrates it The inferior hypophysial arteries arise from the internal carotids in the cavernous sinuses and

supply the processus infundibuli or lobus nervosus by entering its free pole and breaking up into a capillary bed

In addition to the systemic veins which will be described the adult human hypophysis is supplied with portal venules[47,48] These lie beneath the branches of the superior hypophysial arteries for the most part They arise by a confluence of small vessels on the surface of the infundibular stem and are derived from two sources first from a plexus of capillaries of wide caliber on the surface of the infundibular stem and secondly from a number of arborizing tufts of wide capillary plexuses which subdivide the interior of the infundibular stem Both the deep and the superficial plexuses of the stem drain into numerous portal venules which eventually penetrate the parenchyma of the pars distalis and end in its sinusoids Thus the sinusoids of the pars distalis resemble those of the liver in that they are supplied by arterial and venous afferent vessels

According to Wislocki and King[1] the portal venules are not continuous with the vascular supply of the hypothalamus except in so far as the plexiform capillary bed of the infundibular stem connects through the interior of the stem with the capillaries of the general brain net of the hypothalamic region (Fig 14) The vascular transition between stem and hypothalamus is rather abrupt and very few vessels other than these capillary connections bridge the gap Wislocki believes that the direction of blood flow is from hypothalamus to infundibular stem and not vice versa as was suggested by Popa and Fielding[9,60] As quoted subsequently the latter have reported that the portal circulation drains the sinusoids of the pars distalis ascends the stalk and breaks up into a capillary network within the hypothalamic region

The systemic veins consist mainly of lateral hypophysial vessels on each side draining from the adenohypophysis into the cavernous or intercavernous sinuses and of veins which convey blood from the infundibular process into the cavernous sinuses Contrary to the observations of others Wislocki has not observed suprasellar systemic veins accompanying the superior hypophysial arteries

Embryological Aspects of Hypophysial Vascularization — The unique features of the angio architecture of the hypophysis are a result of the way in which the gland is vascularized embryologically According to Wislocki[61] the brain as a whole is ensheathed in a delicate plexus of pial vessels to which arteries and veins can be traced in the 18mm and 21 mm human embryo This pial plexus covers also the base of the diencephalon including the infundibulum and vascularizes the lamina of the undifferentiated mesenchyme which occupies the area between the base of the brain and the epithelial portion of the hypophysis Wislocki has named this network of capillaries the *pial hypophysial plexus* The latter is nourished by arteriolar twigs arising from the internal carotids or the posterior communicating arteries of the circle of Willis These arterioles are des

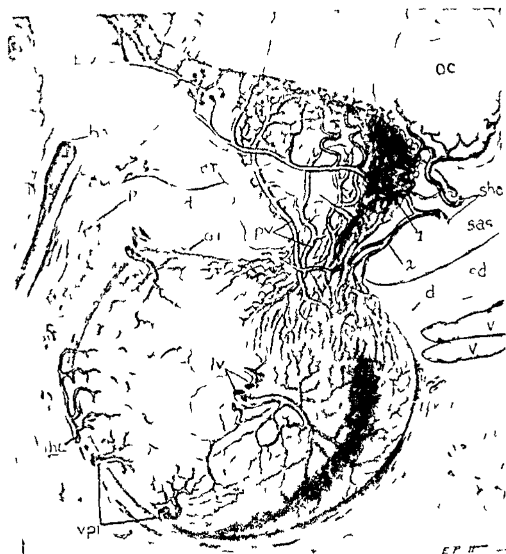


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tined to become the superior hypophysial arteries supplying the pars distalis in addition to sending branches to the pial plexus which surrounds the infundibular stem and vascularizes the latter the tuber cinereum, the pars infundibularis and the pars tuberalis

Beginning with the 25 mm stage of the human embryo the pial hypophysial mesenchyme which develops between the embryonic adenohypophysis and the floor of the third ventricle gives rise to the stroma of the adenohypophysis by invading its parenchyma along well-defined vascular grooves[1] The adenohypophysial parenchyma becomes subdivided finely by this stroma which being extremely vascular, conveys with itself a rich plexus of capillaries arterioles and venules This plexus of vessels soon establishes multiple secondary connections with the venous or cavernous plexuses which occur in the developing dura of the sellar region The pial hypophysial plexus gives rise moreover to the typical sinusoids of the adenohypophysis The secondary connections which are established between the adenohypophysial sinusoids and the cavernous plexuses become the main systemic venous channels of the pars distalis The embryonic adenohypophysis thus acquires a dual venous drainage viz from above through the primary pial venules of the pial hypophysial plexus and from below through the multiple secondary connections which are established with the developing cavernous plexuses The latter are in the mesenchymal region which is to become the sella turcica The primary venous channels from above are destined to atrophy leaving these secondary venous connections the lateral hypophysial veins since the principle efferent veins do not accompany the superior hypophysial arteries in the adult

Because of the attachment of the dura mater to the distal end of the neurohypophysis the processus infundibuli receives its vascular supply from the dura not from the pia mater The inferior hypophysial arteries which are of dural origin penetrate the infundibular process from each side near the midline and break up into its capillary bed The inferior hypophysial arteries arise from the internal carotid arteries in the cavernous plexus The rich vascular bed of the infundibular process drains into a number of collecting veins which emerge from the surface of the gland at various points and then empty into the adjacent cavernous and intercavernous sinuses The arteries and veins of the processus infundibuli being dural in origin, are independent of the vascular supply which reaches the infundibular stem and adenohypophysis from the pial hypophysial plexus

No one knows for certain how the portal venules arise Wislocki has an interesting suggestion in this connection[6,7] He points out that in the adult few if any pial venules connect the infundibulum with the basilar or other pial veins Consequently, the fetal pial venules which drain the embryonic infundibulum and pars distalis must undergo almost complete obliteration It is his belief that

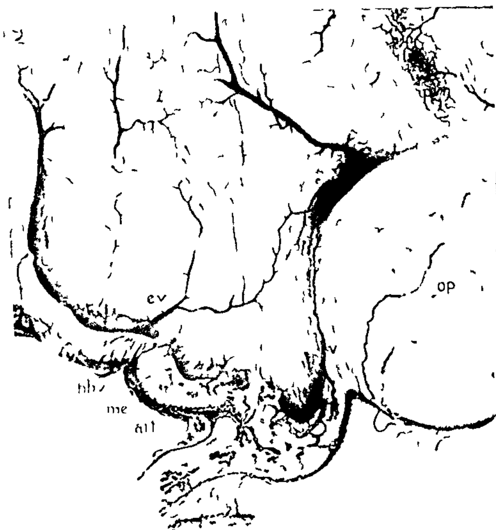


FIG 14 The dissected hypophysial stalk and hypothalamus split in the mid sagittal plane revealing the vascular plexuses within the hypophysial stalk The transitional vessels between the median eminence (me) of the hypophysial stalk and the hypothalamus are shown The largest of these (v) is a vessel of undetermined character A minute arteriole (art) travers ing the boundary of the stalk and hypothalamus is also visible An hypothalamic vein (ev) is seen it passes to the surface and drains into a branch (bbv) of one of the basilar veins It is clear from study of the blood vessels in the transition zone between hypophysial stalk and brain proper shown in this figure that there are no significant vascular links between the hypophysis and the more important nuclear centers of the hypothalamus for example the paraventricular nucleus (pvn) After Wislocki

to the infundibular stem from whence the circulation enters the sinusoids of the pars distalis

The angio architecture of this region may be a clue likewise to the mechanism by means of which the adenohypophysis is stimulated physiologically This is unknown at present although it is well recognized that the neurohypophysis is activated functionally by way of the supra optico hypophysial and tubero hypophysial nerve tracts As compared with the physiological importance of the adenohypophysis on the other hand there is a relative dearth of nerve fibers to which one could *attribute stimulation Humoral stimulation of the pars distalis* could be accomplished however through the portal circulation which undoubtedly collects the products of secretion of the areas it drains Because of the vascular connections *which are known to exist between the capillaries of the general* brain net of the hypothalamus and the infundibular stem it is possible moreover that secretions of the hypothalamic neuronal cells are carried to the pars distalis through these vascular channels

Nerve Supply

Introduction —The gonadotropic functions of the adenohypophysis have been used almost exclusively *to investigate its functional innervation principally* because they lend themselves to experimental study It is a matter of common knowledge that the gonadotropic activities of the adenohypophysis are influenced considerably by the nervous system *From a clinical viewpoint it has been noted* that fear anxiety or indeed any strong emotional experience can interrupt the regularity of the normal menstrual cycle for one or more periods In the laboratory it can be demonstrated that mechanical or electrical stimulation of the cervix uteri of the rat induces a prolonged period of diestrus known as pseudopregnancy presumably because *it initiates a neural stimulus which activates the adenohypophysis* The luteotropic hormone prolactin which is secreted in response to this stimulus thereupon prolongs the functional life of the last formed corpora lutea beyond *that encountered in the normal estrous cycle*

The Cervical Sympathetics —Connection of a Branch of Third Cervical Nerve with the Superior Cervical Sympathetic Ganglion —From an anatomical viewpoint it is reported that postganglionic fibers originating in the superior cervical sympathetic ganglia reach the adenohypophysis through the carotid plexus and end in contact with individual cells [2 8 9] In attempting to trace this pathway physiologically Friedgood[59] noted that a tiny strand of myelinated fibers connecting one of the branches of the cervical plexus third cervical nerve and the *inferior pole of the superior cervical sympathetic ganglion is involved in the* transmission of neural impulses from the cervix uteri to the adenohypophysis

the portal venules which connect the infundibulum with the pars distalis in the adult may represent the modified distal remnants of the pial venules which originally drained the pial hypophysial plexus The concept advanced by Espinasse[5] is quite to the contrary and postulates that the portal venules are modified pial arteries which carry blood from the pars distalis to the infundibulum and hypothalamus Wislocki disagrees vigorously also with Popa and Fielding[6] who have reported that the portal circulation drains the sinusoids of the pars distalis ascends the infundibulum and breaks up into a capillary network within the hypothalamus

The Absence of Lymphatic Drainage — Presumably the hypophysis does not have a lymphatic drainage Clark[c] states that there are no lymphatics in the brain and spinal cord so that the function of absorption must be accomplished by means of the veins Drinker and Field[61] have remarked that lymphatics are found in practically all mammalian tissues with few exceptions, among which are "the depths of the central nervous system

Possible Pathways of Hormonal Secretion and Adenohypophysial Stimulation — No practical purpose can be served by recapitulating the circumstantial evidence and theories which have been recorded in connection with the possible pathways of secretion from the hypophysis Rioch[64] has reviewed the available data in detail One aspect of this problem which surprisingly has received little attention is the relation of the unique angio architecture of this region to the problem of hormonal secretion in general and adenohypophysial stimulation in particular For reasons which will be amplified elsewhere in this chapter, it is essential to regard the hypothalamo hypophysial area as a functional unit

The adenohypophysis is an endocrine organ and as such probably empties its secretion directly into the circulation Since its dense plexus of sinusoids drain through the lateral hypophysial veins into the cavernous sinuses and through them into the systemic circulation it is reasonable to assume that the hormonal secretions of the pars distalis leave the gland through this pathway So far as the constituent parts of the infundibular system are concerned there are two vascular channels which merit consideration In the first place the direction of the blood flow is by way of the portal circulation from the median eminence, pars tuberalis, pars infundibularis and infundibular stem into the sinusoids of the pars distalis If all or a part of the hormonal secretions of these parts of the hypophysis leave the sinusoids of the pars distalis the efferent blood vessels must direct them into the systemic circulation via the cavernous sinuses Secondly, it is possible although unlikely that another secretory pathway is established through the connections of the plexiform capillary bed of the infundibular stem with the capillaries of the general brain net of the hypothalamic region It is more probable, however that the blood flow is in the opposite direction i e from the hypothalamus

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Electrical stimulation of the rat's cervix induced pseudopregnancy in 76 per cent of normal animals in 88 per cent after bilateral cervical sympathectomy in 56 per cent after bilateral superior cervical sympathetic ganglionectomy and in 44 per cent after resection of the cervical sympathetic trunks and the third cervical ganglion nerves It is now clear that the superior cervical sympathetic ganglia are not essential to the mechanism of hypophysial gonadotropic activation, although apparently they are involved in it to some extent, possibly in connection with the third cervical ganglion nerves[69 70]

The Vidian Ganglia and the Greater Superficial Petrosal Nerves —Some of the nerve fibers which pass from the carotid plexus to the hypophysis, are of other than cervical sympathetic origin[71] Chorobski and Penfield[3] have demonstrated the existence of a bundle of small myelinated and non myelinated fibers, which forms a part of the nervus intermedius of Wrisberg, but which leaves the facial nerve as part of the greater superficial petrosal before joining the carotid plexus Hair and Mezer[74] have investigated this pathway, which was endorsed by Hinsay and Markee as a likely possibility[75] They found[74] that electrical stimulation of the facial nerve at the geniculate ganglion did not induce ovulation in rabbits, nor did bilateral destruction of the facial nerve prevent post coital ovulation Zacharias[76] on the other hand has reported that either bilateral removal of the rat s vidian ganglion or section of the greater superficial petrosal nerves is followed by pseudopregnancy in all operated cases and coincidentally induces an increased insulin sensitivity in 66 per cent of the animals Zacharias regards the vidian ganglion as a source of part of the innervation of the adenohypophysis He originally investigated the nerve supply proximal to the sphenopalatine ganglion[7], because bilateral sphenopalatine ganglionectomy induced pseudopregnancy in 40 per cent of the rats operated on by Rosen, Shelesnyak and Zacharias[78] At the junction of the greater superficial petrosal nerve with the great deep petrosal nerve he found the vidian ganglion from which small branches are distributed to the sixth nerve to the internal carotid plexus, to the sheath and presumably to the parenchyma of the adenohypophysis

The Hypothalamus —Available evidence indicates that the hypothalamus is related functionally in an important way to the gonadotropic activity of the adenohypophysis The literature also contains ample reference to nerve fibers which arise in the hypothalamus and pass down the infundibular stem to the pars intermedia and the infundibular process Cajal[79] Tello[80], Croll[81] and Hair[71] are among those who have reported that a few of these fibers cross over into the pars distalis in certain mammals Brooks[7] has described fibers resembling nerve fibers in the pars distalis of normal rabbits which appear to enter the gland from the stalk likewise he has confirmed Croll s observations All anatomists however have experienced the difficulty, underscored by Rasmussen[8] of demonstrat

ing a significant number of nerve fibers in the pars distalis Whether or not this argues seriously against the functional significance of these fibers is an open question It might be pointed out however that the number of these fibers is relatively small in view of the importance of the gonadotropic activity which they are supposed to initiate and control

Physiological experiments with mated rabbits indicate that at one point in their course the nerve fibers carrying the coital stimulus reach the hypothalamus from whence stimulation of the adenohypophysis is affected How the latter is accomplished still is a matter for speculation Westman and Jacobsohn [3], Haterius and Derbyshire[94] and Harris have found that electrical stimulation of highly localized areas in the hypothalamus results in gonadotropic activation of the adenohypophysis with subsequent ovulation Brooks[7] has demonstrated that in the rabbit coital stimuli to the adenohypophysis are interrupted by resection of the infundibular stem Although Harris[85] and Brooks agree on the general course of this pathway they are not in accord on the systemic and endocrine effects of stem section Harris rabbits refused to mate and their gonads atrophied after transection of the stem whereas Brooks reported that in his rabbits the gonads were histologically normal and that the mating behavior was unaltered after a similar operation The extent to which the circulation to the adenohypophysis is interrupted by transection of the stem may have an important bearing on this discrepancy in the results of supposedly identical experiments As a matter of fact a partial interference with the essential blood supply to the hypophysis might account for Brooks results although Brooks believes that his observations constitute evidence for the existence of a neural pathway from the hypothalamus through the infundibular stem to the adenohypophysis Friedgood[69] has suggested that a humoral component arising in the hypothalamus or in the glandular tissues drained by the portal circulation of the infundibular or tuberal structures may be an important part of the mechanism which activates the gonadotropic function of the adenohypophysis

Clinical Interpretation of Phylogenetic Data

Introduction

It has been customary for the clinician to regard the hypophysis as a gland of internal secretion which from a physiological viewpoint is related closely to the other endocrine organs of the body The fact that the anatomical relations between hypophysis and cerebrum are so intimate was of interest almost exclusively to the embryologist and comparative anatomist although certain aspects of this juxtaposition came within the province of the neurosurgeon and roentgenol

ogist More recently, however, since the physiology of the hypothalamus has come under surveillance the spotlight of clinical interest has been shifted to the reciprocal functional relations, which exist between the hypophysis and the various hypothalamic nuclei and nerve tracts These viewpoints, important though they are individually and collectively, are quite likely to result in a limited con

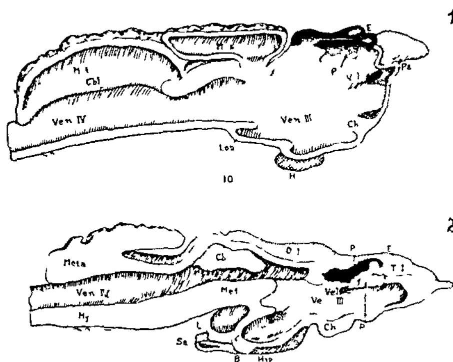


Fig 15 Reconstructions of adult Petromyzon (1) and Amia calva (2) mid sagittal view epi epiphysial complex chi chiasm cbl cerebellum hyp hypophysis loi inferior lobes met metencephalon meta metaphysis my myelencephalon mes mesencephalon lop posterior lobe opl optic lobe par paraphysis per periphysis tel endbrain vel transverse vellum ac accu va culosus vent III third ventricle vent IV fourth ventricle After Tilney

ception of the biological significance of the hypophysis cerebri A more adequate perspective of its biological importance ought to include some appreciation of the phylogenetic relation of the hypophysis to the whole system of cerebral glands, of which it is only one representative

The hypophysis is one of ten cerebral glands eight of which are derived from the roof of the brain and two of which make their appearance in connection with the floor of the brain (Fig 15) In a comprehensive contribution to, and resume

of this subject Tilney states that the endophyses as represented by the lateral mesial and caudal chorioidal glands are the only glandular structures which maintain a definite constancy of histological architecture and function among the outgrowths of the roof of the brain The other five cerebral glandular outgrowths in this group are the paraphysis the periphysis the epiphysial complex the mesophysis and the metaphysis The two glandular outgrowths which are derived from the floor of the brain are the hypophysis and the saccus vasculosus In contrast to the inconstancy which is observed in a phyletic study of the development and degree of specialization of most of the roof glands the hypophysis and saccus vasculosus are represented constantly in the vertebrate phylum from the earliest of cyclostomes through the highest of primates

Glandular Structures of the Roof of the Brain

The outgrowths of the roof of the brain have numerous interesting features a detailed discussion of which is quite beyond the scope of this writing These cerebral structures have two characteristics in particular however which merit special consideration All of them show a typical glandular structure at one time or another in their phyletic history and one or more of them is responsible for the secretion of the cerebrospinal fluid Of the eight cerebral glands which are derived from the roof of the brain only the three chorioidal structures maintain a constant functional representation in the various phyla and consequently they must be of special biological importance The paraphysis and periphysis are similar in structure to the chorioidal glands but they exhibit only inconstant phyletic representation The present discussion is being limited to a consideration of the chorioidal paraphysial and periphysial cerebral glands

The Lateral Mesial and Caudal Chorioidal Cerebral Glands —In lower animals the roof plates of the telencephalon and rhombencephalon remain undifferentiated and are referred to as the anterior and posterior tela chorioidea respectively In higher vertebrates the ventricular cavities of the brain are surrounded by a thick and massive wall of nervous tissue except in the regions which correspond to the tela chorioidea of the lower forms Here the wall retains its embryonic character in the form of a thin non nervous epithelium the lamina epithelialis Adherent to the outer surface of the lamina epithelialis is a highly vascularized pia mater The pial connective tissue and its widely dilated capillaries and venous sinuses invade and indent the tela chorioidea early in its ontogenetic development thus throwing it into crumpled folds and tufts These are invaginated into the ventricular cavities so that a relatively large free surface with branching villus like processes of tortuous vessels and a rich capillary net is exposed to the ventricular system and its fluid These are the chorioid plexuses

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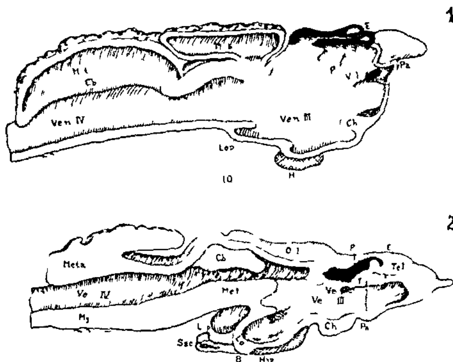


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It is now generally recognized on the basis of embryological histological pharmacological pathological and clinical observations that the cerebrospinal fluid is formed by the chorioid plexuses of the brain ventricles [87 88 89 9 91] Weed[9 93] has demonstrated that the formation of cerebrospinal fluid in the embryo appears coincidentally with the differentiation of the chorioid plexus from the ependymal cells Faivre[94] and others who have confirmed him[95 96 9] have presented evidence of the secretory character of this epithelium The epithelium of the chorioid plexus acquires a unique structure early in its development which differs from that of the ependymal cells lining the ventricles The chorioidal epithelium contains glycogen and carries cilia in its embryonic stages In the adult its cells are cuboidal and are arranged in a single regular layer with definite internal and external limiting membranes (Fig 16) They contain a varying number of rod shaped and granular fuchsin staining bodies which appear to be mitochondria and a round central nucleus Large transparent vacuoles or large usually single fat droplets are very common inclusions in the distal part of the cells Some investigators have observed a brush border on the free surface of these epithelial cells The epithelium of the chorioid plexuses is said to store large amounts of trypan blue in granular form after repeated intravenous injections of the dye into animals

The autonomic innervation of the chorioid plexus has been studied by Clark[98] and Stohr[9] who observed that the nerves penetrated to the epithelial layer and ended on the epithelial cells The latter may be of functional significance but there is no evidence available on this point Finesinger and Putnam have demonstrated that stimulation of the cervical sympathetics causes constriction of the vessels of the chorioid plexus in the cat, whereas stimulation of the vagus leads to their dilatation

From a phyletic viewpoint Minot [1] suggests that the roof of the primitive forebrain gives rise to a series of secreting structures which are directly connected with the formation of fluid in the cavities of the brain In his opinion the chorioidal glands supply the main bulk of this fluid

The Paraphysis —The paraphysis (See Fig 15) is a midline outgrowth from the cephalic extremity of the roof plate of the forebrain It is a structure which is common to all vertebrates either in the adult or in the embryonic state The course of its phyletic development is traced by a curve which rises steadily from the cyclostomes through the fish reaches its peak in the amphibia and descends through the reptiles and birds to its lowest degree of differentiation and specialization in the mammals In the amphibian necturus the paraphysis is a lobulated structure which lies just beneath the pia where it is covered by blood vessels At first it was regarded mistakenly as a part of the chorioid plexus because it was so vascular and so close anatomically to this structure Minot s observations in

which are to be found in the roof of the fourth ventricle, the roof of the third ventricle and in part of the wall of each lateral ventricle When the meninges of the brain are removed at autopsy, the chorioid plexus of the roof of the fourth ventricle may be torn away leaving a large opening, the fossa rhomboidalis The

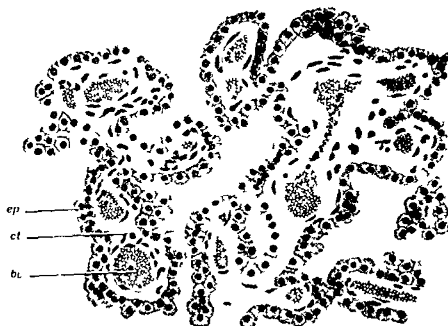


FIG 16 Chorioid plexus of the fourth ventricle from man ep epithelium ct connective tissue bv blood vessels 190 x After Maximow

fourth ventricle communicates freely with the subarachnoid space through the two foramina of Luschka one of which is located in each of its lateral recesses The chorioid plexus of the fourth ventricle extends into each of the latter and protrudes slightly through the foramina of Luschka into the subarachnoid space The mid line third ventricle which leads into the fourth ventricle through the narrow aqueduct of Sylvius also communicates with the lateral ventricles of each hemisphere by way of the foramina of Monro The chorioid plexus of the third ventricle is continuous with that of the lateral ventricles at the foramina of Monro From this point the chorioid plexus extends posteriorly into both lateral ventricles following the curve of the caudate nucleus and fimbriae of the fornix inferiorly and anteriorly to the tip of the temporal horn The anterior and posterior horns of the lateral ventricles do not contain a chorioid plexus

kind or period of life but have been common to all vertebrates from the beginning to the end of their history It is this keystone position which the hypophysis and saccus vasculosus occupy The activities of these organs have constituted an unchanging stream of endocrine function Their long established structural constancy is indicative of their indispensable nature just as their complex differentiation implies the possibilities of widespread tropic influences

Physiological Significance of the Cerebral Glands from a Phyletic Viewpoint

In a comprehensive discussion of the phyletic and embryological aspects of roof glands of the brain Tilney leaves untouched the problem of their physiological significance except in so far as he points out that certain of these structures are concerned with the formation of cerebrospinal fluid

There are two opposing theories concerning the method of formation of the cerebrospinal fluid Faivre[94] and Luschka[9] claimed that it was secreted by the parenchymal cells of the chorioid plexus whereas Mestrezat[108] maintained that the chorioid plexus acts as a dialyzing membrane and that the cerebrospinal fluid is a dialysate in equilibrium with the blood plasma There are a number of telling points against the dialysate theory The latter does not account for the histological tructure of the cells of the chorioid plexus nor for the changes that take place in these cells during conditions which induce a more rapid formation of cerebrospinal fluid Moreover the composition of the cerebrospinal fluid i not identical quantitatively with that of filtrates produced artificially or with dialysates of plasma although the cerebrospinal fluid is isotonic with blood plasma and tends to remain in osmotic equilibrium with the blood when the latter is altered experimentally or by disease[109 1 0 111] Furthermore the dialysate theory does not explain the unequal di tribution between blood plasma and cerebrospinal fluid of calcium, potassium phosphate uric acid creatinine amino acids glucose ard magnesium[112] nor does the distribution ratio of sodium chloride and bicarbonate between plasma and cerebro pinal fluid satisfy the Donnan theory quantitatively The fact that variations in the plasma level of glucose urea chloride lactic acid and alcohol are associated with parallel changes in the cerebro pinal fluid suggests that these substances are subject to filtration On the other hand the distribution of ingested bromide between blood plasma and cerebro pinal fluid is not readily explained by the dialysate theory

In view of certain of the foregoing data, and because there are volume and pressure changes in the cerebro pinal fluid in response to hydrostatic and osmotic variations in the blood one must assume that osmotic and hydrostatic forces play a role in the formation of the cerebro pinal fluid Contrary to general belief however there is no evidence to warrant the assumption that the cells of the

rana[101] have disclosed that the paraphysis has an epithelial structure, a tubular arrangement and a sinusoidal circulation. The glandular character of its parenchyma is obvious in all other forms which have been studied[10, 103, 104, 105, 106, 107]. Tilney suggests that the glandular specialization of the paraphysis indicates clearly that it may provide a secretion of special chemical substances for the cerebrospinal fluid.

The Periphysis. — The periphysis (Fig. 15) is a highly vascular paired outgrowth from the roof of the forebrain, which develops from the dorsal sac just caudal to the paraphysis. It is a large sac-like structure, whose thin convoluted walls consist of one or two layers of epithelium with many irregular communicating diverticulae. In general the sacs resemble the chorioidal glands and are surrounded by a rich vascular network formed by a plexus of capillaries. The periphysis reaches its peak of development and differentiation in the ganoids or fish, but it may be recognized in vestigial form among amphibia, reptiles, birds and man.

Glandular Structures of the Floor of the Brain

The Hypophysis and Saccus Vasculosus. — In other sections of Part I the reader will find a fairly complete account of what is known concerning the ontogenetic development of the hypophysis and saccus vasculosus. The phyletic aspects of this subject matter have been dealt with in detail by Tilney[1]. For our present purposes it is adequate to record a summary of Tilney's lucid thoughts in this direction.

It is relatively simple to trace the different parts of the hypophysis cerebri and saccus vasculosus through the entire line of vertebrates, in each of which they maintain a high degree of specialization. The constant representation of the hypophysis throughout this phylum is equally true of its occurrence, of its origin and development, of the biotaxis of its neural and somatic ectodermal anlage, of its relations to the brain and skull and of the final differentiation of its structure and cellular constituents. The regularity with which these complicated and relatively numerous structural elements reappear throughout this phylum is suggestive of a specific functional significance even though certain minor variations in pattern do occur.

Tilney believes that "the contrast between the variability of the cerebral glands connected with the roof of the brain and the constancy of the floor glands has undeniable significance. On the one hand the glandular specialization bespeaks an adaptive differentiation to meet the exigencies of life peculiar to a species, a family or order of animals; on the other, this specialization is in the interest of certain dominating themes of existence which are confined to no single

kind or period of life but have been common to all vertebrates from the beginning to the end of their history It is this keystone position which the hypophysis and saccus vasculosus occupy The activities of these organs have constituted an unchanging stream of endocrine function Their long established structural constancy is indicative of their indispensable nature just as their complex differentiation implies the possibilities of widespread tropic influences

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chorioidal plexus do not secrete a significant proportion of the cerebrospinal fluid As a matter of fact the available phylogenetic data support this possibility strongly

In general it is important to note that, by definition, all of these cerebral structures are glands of internal secretion at one or more points in their phyletic history Although this has not been established physiologically as yet the histological evidence is consistent with this interpretation, inasmuch as these structures are characterized by a typical secretory parenchyma Moreover it is of significance in this connection that several of the cerebral glands, which take origin from the roof plate of the forebrain are responsible for the secretion of the cerebrospinal fluid The cerebrospinal fluid may be regarded therefore, as the product of a gland of internal secretion even though its rate of secretion may be affected by hydrostatic and osmotic variations in the blood plasma This conclusion which is suggested by the phylogenetic data indicates that the cerebrospinal fluid may have a hormonal action in addition to discharging the excretory nutrient and mechanical functions which have been ascribed to it heretofore Whether or not this hypothesis is established by future investigations is of small consequence as compared with the conception that clinical correlations between structure and function may be found among the observations recorded by students of phylogeny

The phylogenetic history of the chorioidal cerebral glands, which are as constantly represented in the various vertebrates as the hypophysis itself may hold biological secrets which are unfathomed as yet If the advances which have been made in the physiology and biochemistry of the hypophysis are any indication, there is much promise in the further search for the endocrine functions of the other cerebral glands

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Part II

CYTOPHYSIOLOGY AND BIOCHEMISTRY OF THE ADENOHYPOPHYSIS

Adenohypophysial Cytology and its Functional Significance

Cell Types

The foregoing embryological studies have disclosed that a complex glandular organ consisting of pars distalis pars intermedia pars infundibularis and pars tuberalis develops from an undifferentiated stomodeal epithelium The embryonic *cells of these glandular divisions differentiate into specific and characteristic cell* types which include the chromophobes acidophiles and basophiles The cytoplasm of the chromophobes is devoid of granules the cytoplasmic granules of the acidophiles have a strong affinity for the acid dyes and the cytoplasmic gran*ules of the basophiles take the basic dye but their granules are less distinctly* tinted and are more irregular in outline and size than those of the acidophiles[1] [9] The four subdivisions of the adenohypophysis exhibit somewhat similar cytological characteristics but certain individual variations of possible importance have been recognized

Pars Distalis — According to Tilney the pars distalis is comprised of two distinctly different regions viz an outer cortical zone and an inner or central core which is almost completely invested by the cortex The histological dif*ferences between the two portions of the pars distalis are said to be distinct In* general the cortical zone has a much lighter staining reaction and consists essentially of basophiles among which are scattered numerous chromophobes The cellular arrangement is in the form of large acini and extensive interacinal cell masses The medullary or central zone consists of smaller and more compact acini and the interacinal cell masses are more limited The individual cells stain more deeply than those in the cortex and are acidophilic predominantly The cells in both zones are polygonal in shape and the acini of which they are a part are surrounded completely by a connective tissue capsule

Pars Intermedia — The parenchyma of the pars intermedia is the smallest part of the human hypophysis comprising 0 13 to 3 64 per cent of the total hy

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Cell Counts

Although the three cell types occur in definite proportions there is great individual variation in this respect as well as in the arrangement and location of the cells within the pars distalis of the adenohypophysis Consequently cell counts must be made in accordance with statistical methods Rasmussen s classical studies for the human gland[14 3] show that for the adult male the average normal proportions of cells are 5 2 per cent chromophobes 36 8 per cent acidophiles and 10 9 per cent basophiles In different individuals the chromophobes varied from 34 to 66 per cent and acidophiles from 23 to 59 per cent and the basophiles from 5 to 27 per cent In the adult female the average normal proportions of cells are 49 6 per cent chromophobes 43 4 per cent acidophiles and 7 per cent basophiles The chromophobes vary from 33 to 74 per cent the acidophiles from 19 to 58 per cent and the basophiles from 3 to 16 per cent The relative proportions of cells in most species is approximately the same These data indicate that the basophiles constitute less than 10 per cent of the cells in the pars distalis and are significantly more numerous in males than in females The acidophiles represent about two fifths of all the cells and are definitely more numerous in females The chromophobes account for about 50 per cent of the total cell count The males have slightly more chromophobes than the females Although this sex difference is small it is just significant statistically

Statistical surveys of the cell population and specific cytological methods have disclosed that certain physiological states are associated with a significant shift in the relative proportions of the three cell types and that physical changes occur in the cells themselves at these times Such deviations from the normal have been noted after castration during and after pregnancy[5] and after thyroidectomy[8] Changes in cytoplasm and cell proportions likewise have been correlated with the estrus cycle [5 2 3] and with secretion of the luteinizing and lactogenic hormones[15 8] and after the parenteral administration of various hormones to normal and abnormal animals Observations such as these have contributed also to a better understanding of the complex genetic interrelations of the three cell types

Interrelations of Chromophobes Acidophiles and Basophiles

The rarity of mitotic divisions in the adenohypophysis precludes the development of enough hyperplasia to change the relative proportions of cells It is generally believed therefore that one specific cell type changes into another but there is still considerable controversy about the modus operandi of this transformation The most convincing evidence favors the theory according to which the chromo

pophysis according to Rasmussen[9] It is bounded anteriorly by the hypophysial cleft which is open in the human during childhood and adolescence but becomes subdivided later into numerous loculi of different size by trabeculae of flattened cuboidal epithelial cell These loculi become filled with secretion from tubulo racemose glands which arise in the pars intermedia and invade the processus infundibuli Further details of related histological data will be found in the section on neurohypophysial cytology in Part V

There are several other types of cells in addition to those which comprise the epithelium of the hypophysial cleft and tubuloracemose glands Basophilic cells constitute the major portion of the parenchyma and are arranged in long columns or cords which interdigitate with the neurohypophysial tissue in many areas The virtual absence of acini or aciniform grouping of cells also characterizes this part of the gland Chromophobes and acidophiles are scattered among the basophiles The latter occur particularly among the ciliated cells which have been described in the human as well as the subhuman species by Peremeschko[10], Kiyono[11], Guizzetti[1] Bryant[13] Rasmussen[14] and Friedgood and Dawson[15] Another cell seen in the pars intermedia is the so called ependyma like cell[16 1 18 19] It is impregnated best by Golgi s method and consists of a small ovoid nucleus midway between its two extremities Two processes extend from the cell body, one in the direction of the anterior and the other toward the posterior boundary of the pars intermedia

Pars Infundibularis — The cellular constituents of this subdivision of the adenohypophysis have not been studied adequately enough to warrant more than passing comment Without differentiating pars intermedia from pars infundibularis Tilney[7] states that the latter is composed only of basophilic cells

Pars Tuberalis — The pars tuberalis is equal or nearly equal in size to the pars intermedia according to the quantitative studies of Atwell Its general histological structure appears to be that of a coarse network of cell cords and in some animals a striking feature is the presence of numerous alveoli The author has not encountered a clear cut statement on this latter point with reference to the human hypophysis Chromophobes constitute the predominant cell type, although basophiles also are present and acidophiles are rare Wolf and Cleveland [1] and Dawson and Friedgood point out however, that the physiological state of the hypophysis may determine whether chromophobes or basophiles predominate In the rabbit occasional acidophiles and numerous basophiles are to be found in the tongue like projection of the pars tuberalis as it passes toward the hypothalamus in front of the infundibular stem[15]

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phobes are transformed either into acidophiles or basophiles through the accumulation of the corresponding specific granules[6,3,7]. Apparently certain chromophobes are themselves so highly type specific that they give rise only to one or the other of these chromophilic cells. There is no evidence to support the belief that a transitional bigranulated cell exists or that an acidophile can change into a basophile or vice versa. If the chromophilic granules of a given cell should be interchangeable, it is believed that this transformation must occur during the stage of the undifferentiated chromophobe[19].

Physiological Significance of Chromophilic Granulation. Theories of Hormone Elaboration and Secretion

The transformation of chromophobes into chromophilic cells and vice versa is associated with a change in the physiological state of the organism; the presence of chromophilic granules indicates that the cell is functionally active, whereas the chromophobe represents an inactive reserve or parent cell. It is believed generally that the chromophilic granules represent the hormone either in a stored or active form and that degranulation of a cell occurs coincidentally with the phenomenon of secretion. Direct evidence on this point was secured by Friedgood and Dawson[15,31,3] in connection with their observations on the elaboration and secretion of the luteinizing hormone from the adenohypophysis.

Of the large number of adenohypophysial hormones which have been postulated, only seven are accepted generally. These are the growth hormones, the follicle stimulating, luteinizing and lactogenic hormones, the thyrotropic hormone, the adrenocorticotropic hormone and the diabetogenic hormone. Since these numerous tropic substances are elaborated only by the basophiles and acidophiles, the situation often is viewed with considerable despair and incredulity. However, if one considers the accomplishments of the hepatic cell which is concerned with the most complex of chemical activities affecting every known phase of metabolism, the performance of the adenohypophysial chromophiles is not uncommonly spectacular. Apparently a number of independent, albeit related and integrated, biochemical and physiological activities may coexist in a highly differentiated cell.

Relatively little is known concerning the chemistry of the adenohypophysial hormones and practically nothing has been discovered of their chemical interrelations and elaboration. They could be manufactured and secreted as chemically independent molecules, they might be attached to a large protein molecule in the form of prosthetic groups, or one hormone could affect a number of different endocrine glands depending on the specific end organs or target glands with which it came into contact. The latter possibility can be eliminated from consideration because of the fairly quantitative chemical separation of the lactogenic

thyrotropic somatotropic and gonadotropic hormones If the second hypothesis represents the true state of affairs an unusual demand for one of the hormones would be answered by the indiscriminate overproduction of several other tropic substances *which happen to be attached to the same protein molecule* Such an inelastic physiological mechanism always would create overfunction of a number of related endocrine glands to the disadvantage of the organism as a whole There might be one conceivable advantage to such a system viz if the metabolic demands created by hyperactivity of one target gland could be maintained only by increasing the functional activity of several other intimately related glandular structures

As a matter of fact this multiple type of response is encountered not infrequently in various clinical disorders of the hypophysis of which acromegaly and the menopause are good examples In acromegaly the primary disability is caused by an overproduction of the somatotropic hormone with which often there is associated an abnormally increased secretion of the diabetogenic hormone the thyrotropic hormone and the ICSH or luteinizing hormone resulting in diabetes mellitus hyperthyroidism and hypergonadism respectively The primary adenohypophysial dysfunction of the menopause is expressed in terms of overproduction of the follicle stimulating hormone but hyperthyroidism and diabetes mellitus not infrequently are concomitant complications of this condition These complex endocrine patterns of activity can be explained also on the basis of the first hypothesis inasmuch as the activation of one phase of a cell s metabolism might conceivably result in hyperactivity of a closely related but chemically independent functional unit of the same cell The clinical cour e of disordered function of the acidophiles in acromegaly actually favors the first hypothesis since the thyrotropic and gonadotropic functions of the e cells are not necessarily disturbed in the same direction nor at the same time It is possible therefore that a single cell type may elaborate a number of metabolically and chemically related hormones which are secreted independently as the occasion demands This hypothesis would explain satisfactorily why a disturbance in the elaboration and secretion of one of these hormones may on occasion induce repercussions in the metabolism and secretion of other hormones which originate within the same cell

The Gonadotropic Hormones

Chemistry

The three adenohypophysial secretions which contribute to the regulation of gonadal function are the luteinizing follicle stimulating and lactogenic hormones Significant progress has been made in their chemical characterization but still

there is much to be learned Although chemically impure these substances can be separated from each other and from the remaining known adenohypophysial hormones in highly purified states The follicle stimulating hormone, also known as FSH or thylakentrin appears to be a glycoprotein with an isoelectric point at about pH 4 8[4] Chemical analyses of the luteinizing hormone, otherwise referred to as LH, metakentrin interstitial cell stimulating hormone or ICSH, are being done on sheep and swine hypophyses by three groups of investigators A highly purified glycoprotein has been isolated from each animal, but the chemical characteristics of these substances are unlike enough to indicate the presence of two different proteins The sheep protein, isolated by the University of California group contains 4 5 per cent mannose, 5 8 per cent, glucosamine, 1 per cent tryptophane 4 5 per cent tyrosine and 5 4 per cent cystine Thus far it has been found that the swine protein isolated by the Rockefeller Institute and Squibb groups contains only 2 per cent carbohydrate and 3 8 per cent tryptophane The isoelectric point of the sheep protein is at pH 4 6, while that of the swine protein is at pH 7 4[11] The lactogenic hormone also called prolactin galactin and mammotropin was the first adenohypophysial substance to be secured in a highly purified state A crystaline protein has been obtained from a highly purified preparation of the lactogenic hormone[4] In the case of proteins, however the crystalline state is not considered adequate evidence of purity The electrophoretic behavior solubility studies and ultracentrifugal analysis of a highly purified amorphous preparation of prolactin indicate that it is a homogenous protein[12] The isoelectric point appears to be at about pH 5 65[13] The crystalline and purified preparations of prolactin give the usual protein color tests viz biuret xanthoproteic Millon s and Hopkins Cole The labile sulfur test is positive, qualitative tests for phosphorus and for carbohydrates are negative There is no indication of the presence in the molecule of any of the common types of prosthetic groupings Beef prolactin contains 51 50 per cent carbon 6 92 per cent hydrogen 16 50 per cent nitrogen 2 00 per cent sulfur, 5 7 per cent tyrosine, 1 3 per cent tryptophane and 3 4 per cent cystine

Physiology

The Follicle stimulating and Luteinizing Hormones — The follicle stimulating hormone also known as FSH or thylakentrin is a gametogenic substance, which is essential for the growth of graafian follicles and stimulates the sperm forming tissue of the testes[44 4 46] Acting in conjunction with FSH is the luteinizing hormone also known as LH ICSH or metakentrin which is essential for the secretion of estrogens from the ovarian follicles[47 48 49] and for the various consecutive phases of follicular development including the primordial follicular antra

the progressive preovulatory enlargement of the ovarian follicles ovulation and the formation of luteal tissue and corpora lutea [16, 35, 5] The luteinizing hormone is not the factor however which maintains the corpora lutea in a functional secretory state another adenohypophysial luteotropic factor prolactin is responsible for that function [4, 57, 58] A highly purified fraction of follicle stimulating hormone containing traces of luteinizing hormone induces the development of normal estrous follicles and mating behavior in young adult anestrous cats [9] In the male LH acts on the interstitial cells of the testes stimulating them to secrete the male hormone which then maintains the secondary sex structures and characteristics of the organism[61]

That the gonadotropic hormones of the adenohypophysis may be involved in the development of ovarian tumors in the hen which resemble the arrhenoblastomata of women is suggested by studies of the ovaries of hens in whom sex reversal occurred spontaneously[6] Available evidence indicates that the growth of these tumors in the hen was induced by the pathological destruction or atrophy of the left ovary which is equivalent to complete castration in this animal It is believed that the latter is responsible initially for hypertrophy of the adenohypophysis The subsequent increase in secretion of the gonadotropic hormones stimulates the vestigial cells of the atrophied medulla of the right ovary which becomes active functionally The androgenic effect of the ovarian secretion thus induced culminates in the sex reversal[60]

The Luteotropic Hormone — The chief functions of prolactin were thought originally to be crop gland proliferation in pigeons and initiation of lactation in mammary glands possessed of a certain degree of alveolar development [3, 64, 65, 66, 67] Subsequent studies have indicated however that there is an increased secretion of the adrenocorticotropic hormone as well as prolactin subsequent to pregnancy[68] The initiation of lactation apparently depends on the synergistic action of prolactin and a hormone of the adrenal cortex[65, 6, 7, 8] Prolactin has been shown to exhibit a number of other effects but the latter are species specific in many instances and cannot be transferred from pigeons on which most of the studies have been done to the various mammalian species [6] More recently it has been demonstrated that prolactin has a luteotropic function whereby it maintains the functional integrity and secretion of the corpora lutea which otherwise would regress under the influence of LH alone[56, 57, 58, 7]

Cytology in Relation to Secretion

The Castration Cell — Ablation of the ovaries or testes is followed regularly by an increase in the size and number of the basophiles in the adenohypophysis of the rat guinea pig rabbit goat monkey and man [4, 32, 73, 74, 5] The cytoplasm

of certain of these enlarged basophiles becomes vacuolated and is displaced by a colloid like material which also pushes the nucleus to one side This cytological change imparts the typical appearance to the so called "castration cell" or "signet ring cell [73, 4] which does not develop in some species, such as the guinea pig rabbit and man The physiological castration, which comes with advancing years in men and women likewise is associated with a significant increase in the percentage of basophiles [4]

Surgical and physiological castration also affect the acidophiles of the various aforementioned species including man The acidophiles are somewhat decreased in number and show regression toward the chromophobic state with a decrease in their size and staining capacity [3, 76, 7, 78]

The physiological significance of these cytological changes has been disclosed by a number of investigators in the course of quantitative and qualitative studies of the gonadotropic hormone content of the adenohypophysis of the blood and of the urine in the post castration period The gonad stimulating potency of the adenohypophysis of the castrated rat guinea pig and rabbit was found to be increased [9, 80, 81, 82, 83, 84, 8, 86] It was demonstrated, furthermore, that castration greatly increases the FSH but does not alter significantly the LH content of the adenohypophysis[87, 88, 89, 90, 91] A sex difference with regard to the latter was reported by Lipschutz and Villogran[9] who observed that castration does not change the luteinizing power of the male hypophysis, which already is rich in LH, but does increase it in the female in which normally it is very low

This increase in the FSH content of the adenohypophysis is associated with the appearance in the blood and urine of larger than normal amounts of FSH Experiments with parabiotic rats[87] show that the hypophyses of castrated males secrete chiefly the follicle stimulating hormone FSH Emery[93] demonstrated FSH in the serum of castrated rats but could not find it in their urine with his technic Jeffcoate[94] found FSH in the urine of 3 out of 5 castrated rabbits Fluhmann[95, 96, 97] discovered significantly increased levels of FSH in the serum of castrated and menopausal women Zondek[98] and Saethre[99, 100] demonstrated relatively large amounts of FSH in the urine of castrated and menopausal women respectively, and Hamburger[101] and Osterreicher[10] reported similar results for castrated and elderly men respectively Fluhmann and Hamburger emphasized that their extracts were predominantly follicle stimulating with negligible luteinizing qualities With extremely high doses it has been demonstrated however that luteinization of the ovaries of hypophysectomized rats can be induced by extracts of the blood and urine of castrated and menopausal women[103]

Correlation of the foregoing cytological and physiological data indicates that FSH is secreted by the basophiles The cytological appearance of the basophiles is, however more compatible with an increased accumulation of hormone rather

than with an acceleration in the rate of liberation of their secretion. Consequently it is probable that the relatively large number of secreting basophiles in the hypophysis *of the castrated individual is responsible for the excessive amounts of* FSH which appear in the blood and urine after castration or during the menopause. One must conclude also that small amounts of LH still continue to be released from the hypophysis of castrated individuals. Although the source of FSH is generally agreed upon, there is relatively little in the literature on the origin of LH and prolactin. Friedgood and Dawson[15, 74, 85] have demonstrated, however, that LH is secreted by an acidophilic type of cell, and their circumstantial evidence *indicates that prolactin is derived from a cell with identical morphological* characteristics.

The Carmine Cell. — The origin of LH was traced directly to the acidophiles by correlating the sequence of cytological and physiological events in the adenohypophysis with the characteristic effects of this hormone on the mature ovarian follicles of the cat and rabbit.[5, 84, 3] The hypophyses were subjected to formol sublimate fixation followed by differential staining with Heidenhain's azan modification of Mallory's connective tissue stain. Although the morphological appearance of the acidophile which secretes LH differs remarkably from the ordinary acidophiles, it is not a new type of cell except in so far as it represents a hitherto unrecognized functional phase of the secretory cycle of the acidophiles. When fixed and stained with the aforementioned technic[1, 4] this cell takes a deep dark red stain, whereas the ordinary acidophiles are orange, the basophiles are deep or light blue, and the chromophobes are light pink to colorless. Because the cell contains large coarse irregular granules with a striking affinity for the azocarmine dye, which is extracted readily from the ordinary acidophile, it has been named the carmine cell. The conditions under which it was discovered are somewhat as follows.

Rabbits normally ovulate 10 to 12 hours post coitum and ovulation does not occur spontaneously in this species. It has been demonstrated that post-coital ovulation can be prevented if (a) the infundibular stem is severed prior to mating or if (b) the hypophysis is removed within 60 to 90 minutes after mating. Hypophysectomy does not interfere with ovulation if it is done later than 90 minutes post coitum. These observations show that the behavioral phenomena which are characteristic of coitus induce ovulation in the rabbit by virtue of their stimulating effect upon the gonadotropic activity of the adenohypophysis. It has been demonstrated furthermore that the gonadotropic potency of the hypophysis changes abruptly after mating. The adenohypophysis of the average normal rabbit in heat contains 1 560 rabbit ovulating units of gonadotropic substance. *Within the half hour post-coitum there is a 20 per cent* decrease in its gonadotropic potency to 1 2 0 units, and after 4 hours post coitum the potency de

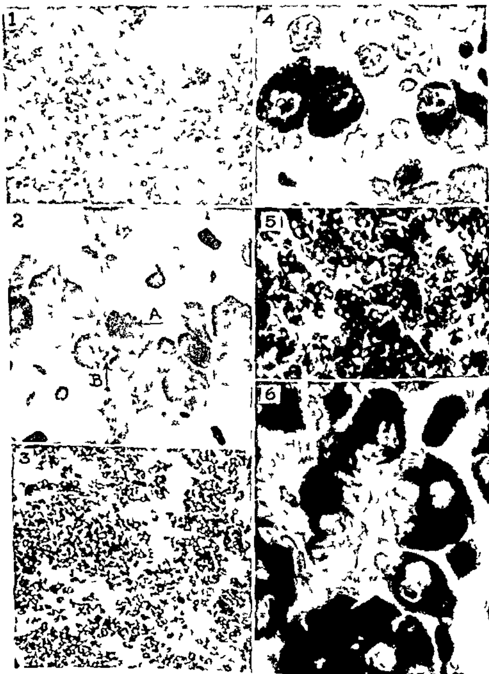


FIG 17 For legend ee page 828 (37)

creases approximately 87 per cent to a value of 210 units[1] These facts indicate therefore that within one and one half hours the adenohypophysis secretes the amount of gonadotropic hormone necessary to accomplish ovulation 10 hours later

Cytological evidence of this adenohypophysial stimulation by coitus was reported by Friedgood and Dawson in 1937[106] They found that the carmine cells are present in moderate number in the adenohypophysis of the estrous rabbit become increased significantly in number within one half hour after mating and reach their peak within 3 hours after which degranulation begins (Fig 17) This increase in number could be detected macroscopically in many instances because of their aggregation into compact irregularly circumscribed areas (Fig 18)

It was demonstrated subsequently that similar cells occur in the hypophysis of the cat an animal which like the rabbit usually ovulates only post coitum (Fig 19) Although morphologically different from those described in the rabbit s hypophysis these cells had an identical affinity for azocarmine Studies of the functional significance of these carmine cells revealed that they were not present in the hypophysis of the anestrous cat (Fig 19 (1) and (2)) They appear first in a limited area of the adenohypophysis during proestrus and then increase significantly in number and extent of distribution during estrus After mating they are arranged in a characteristic alveolar pattern and their greatly increased number and extent of distribution reach a maximum within 5 to 6 hours (Fig 19 (3) and (4)) Degranulation which occurs as early as 4 hours post coitum becomes more pronounced after 6 hours and the carmine reaction is virtually over at 14 hours

More specific information concerning the functional significance of the carmine cell was found in other experiments In most cats coitus normally induces ovula

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An area from the adenohypophysis of a rabbit in estrus showing the characteristic distribution of the carmine cells (black) in an unstimulated gland × 80 (2) A small cluster of carmine cells (dark) with a few orange acidophiles (gray) from an unstimulated gland showing the relative size of the 2 types of cells and the differences in the character of their granulation A lightly stained carmine cell is shown in mitosis (A) Note the distinct macula (B) in 3 carmine cells × 700 (3) An area from the adenohypophysis of a rabbit 1½ hour after mating showing the increase in size and number of the carmine cells and the general pattern of their distribution (cf (1)) × 80 (4) An area from the adenohypophysis of a rabbit in estrus showing the occasional large coarsely granulated carmine cells (black) which occur in association with smaller more finely granulated acidophile cells (gray) × 400 (5) An area from the same gland as (3) showing a dense aggregation of carmine cells with scattered orange acidophiles × 160 (6) An area from an activated gland showing densely stained carmine cells (black) and orange acidophiles (gray) × 700

Tissues in (1) and (4) were fixed in formalin The others were fixed in mercuric bichloride and formalin All were stained by Heidenhain s azan modification of Mallory s method Reproduced from Endocrinology 1938 XXII 674

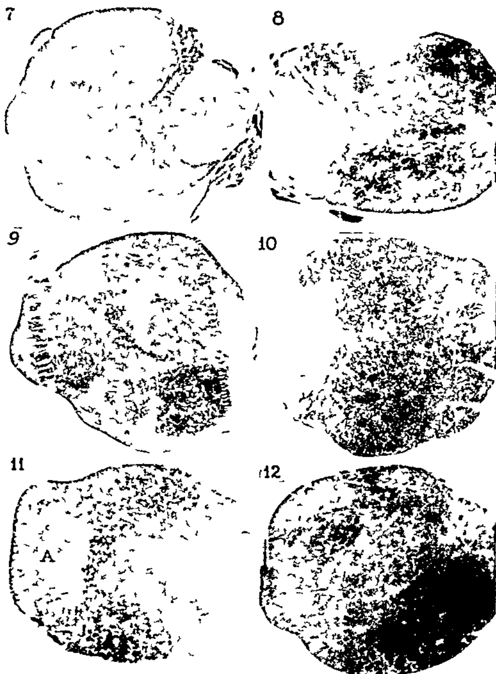


FIG 18 For legend see page 828 (39)

tion within 26 to 30 hours but this does not occur if the animals are subjected to various non-specific abdominal operations shortly after mating[1]. In such circumstances the usual post-coital carmine cell reaction is absent and the number of carmine cells remains at the average estrous level[3]. Furthermore there is a marked delay in the onset of degranulation inasmuch as the granulation of the carmine cells of animals autopsied 48 hours or more post-coitum is comparable to that of the estrous cat. The extent of the carmine cell reaction alone cannot be correlated, however, with the secretion of the gonadotropic substance since a careful study in serial section of the ovarian follicles failed to reveal evidence of activation unless adequate degranulation was observed also. The occurrence and amount of degranulation apparently is the factor which determines whether or not maturation of follicular ova and ovulation will occur. Lack of degranulation of an extensive carmine cell reaction leaves the ovarian follicles in an estrous state; partial degranulation may or may not be associated with minimal evidence of maturation depending on the original extent of the carmine cell reaction; massive degranulation of a widespread carmine cell reaction appears to be essential for completion of maturation and subsequent ovulation.

On the basis of these and other published observations Friedgood and Dawson[15] have concluded that (a) the carmine cell reaction constitutes histological evidence of the enhanced gonadotropic activity of the adenohypophysis which results from coitus; (b) that the carmine cell contains a luteinizing hormone which is essential for the initial maturation and subsequent ovulation of the ovarian follicles; (c) that degranulation represents the secretory phase during which, if the extent of the carmine cell reaction is sufficient and the degranulation adequate, enough hormone is released to initiate maturation and to induce ovulation.

Although these data indicate that in the post-coital period the carmine cells are related to elaboration and secretion of the luteinizing hormone, it is believed[15] that they may be associated also in some way with other gonadotropic functions of the adenohypophysis since they are present in extraordinarily large numbers in the cat's hypophysis during the last week of pregnancy and early lactation.

The Pregnancy Cell.—Contrary to a generally accepted theory,[8] the hy-

(7) A representative section of an unstimulated hypophysis showing the uniformity of the cellular distribution in the pars distalis. × 20. (8) A section from the hypophysis of a rabbit 45 minutes after mating showing distinct and irregular dense areas of carmine cells. × 20. (10) A section from the hypophysis of a rabbit 5½ hours after mating. The cellular aggregations are not so large and distinct. This results in a mottled appearance. × 20. (11 and 12) Sections of other activated hypophyses showing variations in the distribution of the carmine cells. In (11) the median antero-ventral area, zona tuberalis (A), is distinctly outlined. × 20. Black areas represent sites occupied by the carmine staining cells. Reproduced from Endocrinology, 1938, XXII, 6, 4.

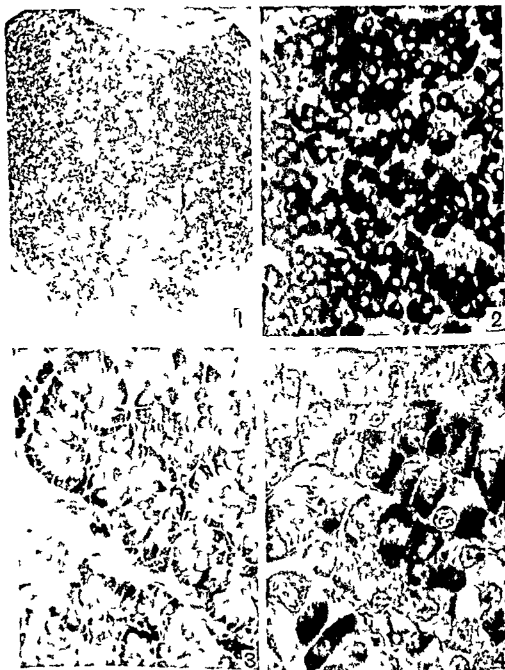


FIG 19 For legend see page 828 (41

pophysis appears to be an actively secretory gland during pregnancy Degranulation of the acidophiles and basophiles numerous mitochondria and hypertrophy of the Golgi apparatus[3 110 11] are clearly indicative of its heightened state of activity As might be expected under such conditions these hypophyses reveal little storage of hormone when tested by implantation At the onset of pregnancy in the rat the acidophiles show degranulation numerous mitochondria and hypertrophy of the Golgi apparatus whereas the basophiles do not appear to be altered significantly Toward the middle of pregnancy however the basophiles become large and granular and during the latter third they show a considerable depletion of their specific granules and a marked increase in their eosin staining mitochondria The latter may be deceptive since it imparts to the basophile the appearance of an atypical bigranular cell[3] Kirkman[1] has reported that the pregnant guinea pig s hypophysis is characterized principally by mitochondria filled degranulated basophiles He observed also a significant increase in the number of acidophiles toward the end of pregnancy and in the post partum period The latter has been confirmed for the full term human hypophysis [3] and has been noted also in the rat [2]

Comte [5] was among the first to recognize a change in the human hypophysis during pregnancy In addition to the increase in size and weight of the gland to which Comte called attention Erdheim and Stumme[1] observed an acidophile like cell which they named the pregnancy cell Their statement that it originated from the chromophobe has been substantiated since then but their belief that it represented a new cell type has not been confirmed by subsequent investigators [3 39 11 114] The pregnancy cell has been described variously as a large finely granulated chromophobe or a small finely granulated acidophile These forms which apparently represent a different state of its activity indicate that it arises from a chromophobe which becomes granulated and degranulated in accordance with a well recognized cycle of secretory function

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Fig 19 (1) Anestrous cat Low power view of mid portion of a frontal section of the adenohypophysis The central area (gray) of basophiles and chromophobes is the zona tuberalis which divides the adenohypophysis into right and left halves The majority of the cells in the latter are ordinary acidophiles (dark) (2) Anestrous cat Medium power view (frontal section) of area from one wing of pars distalis Ordinary acidophiles are dark and clusters of small chromophobes are gray (3) Cat 1 hr 40 min after mating Medium power view (frontal section) of a peripheral area adjacent to the zona tuberalis showing the characteristic alveolar pattern of the carmine cells (dark) Ordinary acidophiles are also present (gray) (4) Oil immersion view of deeper lying area from the same adenohypophysis as (3) showing the distinctly granulated carmine cells (dark) scattered among the more homogenous ordinary acidophiles (gray) (Appropriate filters were used in each instance to achieve the desired contrast between the variously stained cells for purposes of photographic clarity) Reproduced from Endocrinology 1940 XXVI 10 2

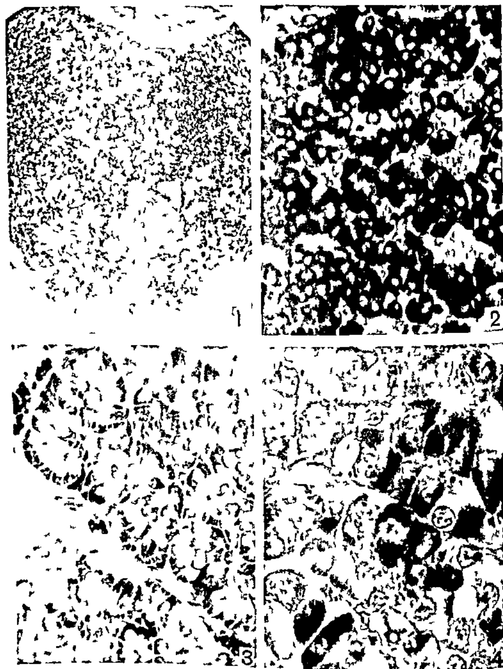


Fig 19 For legend see page 828 (41

decrease of the basal metabolic rate[179 13 133] Appropriate replacement therapy obviates this evidence of functional deterioration[1 1 134]

Injections of acid or alkaline extracts of the adenohypophysis stimulate the functional activity of the normal thyroid gland by virtue of a thyrotropic hormone which has been isolated in highly purified form Such extracts initiate metamorphosis in the larvae of axolotls frogs and salamanders because of the hyperthyroidism which is induced by the thyrotropic hormone [35 136 137 13 39 14 141 14] Injections of extracts containing thyrotropic hormone also bring about similar functional and histological changes in the thyroid glands of birds and mammals as follows

(1) Parenchymal hypertrophy and hyperplasia of the thyroid gland with liquefaction and loss of colloid[1 5 116 143 1 4 14 146 147 1 8 149 1 151 15 1 7 54 1 5 156 15 158 159 1 0 1 16 161] all of which eventually recede in spite of continued injections of the extract[143 153 1 16 163] (Fig 20)

(2) Hypertrophy of the Golgi apparatus and mitochondria of the thyroid gland[157]

(3) An initial increase in basal metabolic rate[134 16 163] which returns spontaneously to its normal level in spite of uninterrupted injections of the extract[16 16 163 16] This rise in basal oxygen consumption can be prevented from the very beginning [15 166 167] or decreased after it has become elevated[166 167 168 69 1 0] by the administration of potassium iodide The rise in basal metabolic rate after the administration of thyrotropic hormone is known to be directly dependent upon the presence of the thyroid gland and cannot be provoked in its absence[158 171] In general however the increased basal metabolic rate which is induced by a chemically crude adenohypophysial extract is due only in part to thyroid stimulation Another more rapidly elicited increase in the rate of oxygen consumption has been noted in fed animals shortly after the injection of such extracts and it is not prevented by thyroidectomy[1 173 174] Riddle and his co workers[173] believe that this calorigenic action is elicited in pigeons by prolactin

(4) Decrease in total and protein bound iodin in the thyroid gland simultaneously with their increase in the blood stream[175 7 1 7 1 1 9]

(5) Exophthalmos in metamorphosing tadpoles [36 137 13] as well as in ducks and guinea pig [5 5 1 16 15] (Fig 21) This exophthalmos can be produced in the absence of the thyroid gland[171 16]

(6) Tachycardia[15 16 87 143] and abnormal nervous irritability in guinea pigs [1 183]

The experimental syndrome induced by such adenohypophysial extracts shows certain interesting correlations between the structure and function of the thyroid gland [16] The intraperitoneal administration to guinea pigs of an extract containing the thyrotropic hormone induces a rise in basal metabolic rate which be

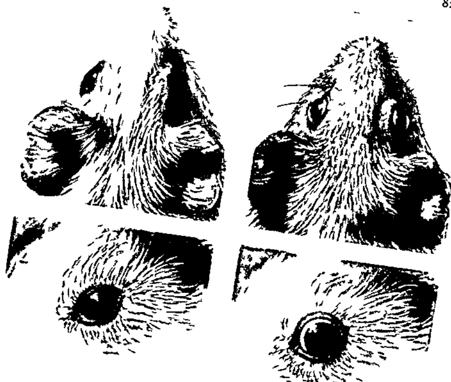
The Thyrotropic Hormone

Chemistry

Janssen and Loeser[11] were among the first to purify the thyrotropic hormone substantially and subsequently Loeser[116] described a method of obtaining a highly active preparation of the thyrotropic hormone in stable dry form. Various substances have been used in the extraction of this hormone, including aqueous solutions of pyridine[11, 11], diethylamine[116], ammonia[11, 118], dilute acetic acid[11] and flavianic acid[1 9]. An extensive study of the purification of the thyrotropic hormone has been carried out recently by Jorgensen and Wade[1 1] and by Bonsnes and White[1]. Starting with an extract prepared by Bonsnes and White[1], White and Ciereszko[1 1 1] studied further the fractionation and isolation of the thyrotropic hormone from beef hypophyses. They developed a method which resulted in the preparation of a protein fraction high in thyrotropic hormone activity and homogenous in both the Tiselius apparatus and ultracentrifuge. The final product of this procedure is a white powder readily soluble in water and precipitated from neutral solutions by the addition of acetone to a concentration of 75 per cent. The preparation gives the usual qualitative protein color tests. The labile sulfur and Molisch tests are positive. Phosphorus is not present. The protein is precipitated from aqueous solution by phosphotungstic acid, picric acid, uranium acetate and mercuric chloride but it is not precipitated by sulfosalicylic acid or by lead acetate. A total of one microgram of this material will produce a minimum histological response in the three day old chick if given once daily for 5 days. This preparation has an approximate molecular weight of 10,000. Similar fractionation studies of sheep hypophyses indicate that the thyrotropic hormone fraction from this source in contrast to that obtained from beef hypophyses is not yet homogenous in the Tiselius apparatus[1 5]. There are at least two protein components present in the most highly purified sheep thyrotropic fractions now available. Bioassays of purified thyrotropic hormone prepared from beef and sheep indicate that the activity of the latter is approximately twice that of the former per unit of weight[1 5].

Physiology

Effects of Hypophysectomy or of Injection of Adenohypophysial Extracts on Structure and Function of Thyroid Gland. — It is well established that the functional state of the thyroid gland can be influenced greatly by the adenohypophysis. Ablation of the adenohypophysis causes a retardation of development or atrophy of the thyroid gland[1, 6, 1, 7, 1, 1, 9, 130, 131], as a result of which there is a significant



[Enlarged]

Fig 21 Upper and lower left Normal appearance of eyes in an untreated guinea pig as seen from above and laterally Upper and lower right Exophthalmos in guinea pig induced by daily intraperitoneal administration of an alkaline extract of the adeno hypophysis Reproduced from Bulletin of the Johns Hopkins Hospital 1934 LIV 48

gins within 18 hours and reaches its peak of 22 to 66 per cent about the seventh or eighth day of the experimental period Exophthalmos appears toward the end of the first week of treatment The thyroid gland shows hypertrophy and hyper plasia of the acinar epithelium and of the mitochondria The Golgi apparatus is hypertrophied The amount of acinar colloid diminishes as the total and protein bound iodin in the thyroid decreases and there is a parallel increase in the con centration of the iodids in the circulation The rise in basal metabolic rate the development of the hypertrophic and hyperplastic changes in the thyroid gland the increase in the concentration of iodin in the circulation and its decrease in the



Fig 20 Thyroid glands from guinea pigs Upper left untreated control Upper right injected daily with chemically crude adenohypophysial extract containing thyrotropic hormone B M R + 40 per cent autopsied on fifth day Lower left similar treatment for 10 days B M R + 100 per cent died of thyrotoxicosis on eleventh day Lower right similar treatment for 18 days B M R + 51 per cent on eleventh day + 25 per cent on eighteenth day when animal died of thyrotoxicosis Reproduced from Bulletin of the Johns Hopkins Hospital 1934 LIV 48

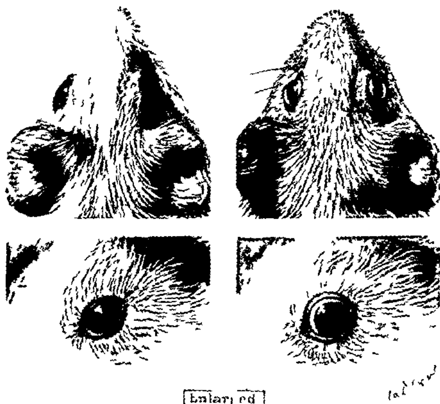


Fig 21 Upper and lower left Normal appearance of eyes in an untreated guinea pig as seen from above and laterally Upper and lower right Exophthalmos in guinea pig induced by daily intraperitoneal administration of an alkaline extract of the adeno hypophysis Reproduced from Bulletin of the Johns Hopkins Hospital 1934 LIV 45

gins within 18 hours and reaches its peak of 2 to 66 per cent about the seventh or eighth day of the experimental period Exophthalmos appears toward the end of the first week of treatment The thyroid gland shows hypertrophy and hyperplasia of the acinar epithelium and of the mitochondria The Golgi apparatus is hypertrophied The amount of acinar colloid diminishes as the total and protein bound iodin in the thyroid decreases and there is a parallel increase in the concentration of the iodids in the circulation The rise in basal metabolic rate the development of the hypertrophic and hyperplastic changes in the thyroid gland the increase in the concentration of iodin in the circulation and its decrease in the

thyroid gland take place coincidentally. Within a week or 10 days a remission in the metabolic disturbance develops in spite of, and because of, the continued administration of the adenohypophysial extract which contains the thyrotropic hormone. The immediate reason appears to be the inactivation of the thyrotropic hormone by the formation of an antibody to its protein content[163, 169, 1, 4]. The basal metabolic rate returns to its normal value within 1 to 3 weeks. Sometimes, however, the decreasing rate of oxygen consumption overshoots its original mark and descends to a hypothyroid level, probably because the thyroid has been emptied of its normal colloid stores. Involution of the parenchymal hypertrophy and hyperplasia and reaccumulation of acinar colloid lag moderately behind the decreasing metabolic rate. By the time the basal metabolic rate has reached its normal level, however, these regressive, histological changes are fairly complete, although the reaccumulated colloid is rather poor in iodin. About 8 per cent. of the guinea pigs studied were resistant to the thyrotropic effects of the extract and revealed a highly curtailed initial increase in the rate of metabolism and a strong tendency toward an early remission[163, 164]. Occasionally a brief transitory secondary rise in the rate of metabolism occurred after such an abortive response. On the contrary, there are other guinea pigs, even less in number, which display only a negligible resistance to the extract, and after a rapid initial increase in the rate of oxygen consumption suffer several marked exacerbations of their hyperthyroidism. Sex is one of the factors that plays a role in the variable response which the thyrotropic hormone elicits. This is significant in view of its similar importance in the clinical syndrome of exophthalmic goiter. Although not an invariable occurrence, the metabolic disturbance is more intense and of longer duration in the female than in the male guinea pig[169, 170].

The metabolic effect of the adenohypophysial thyrotropic hormone is enhanced significantly if its daily administration to tadpoles or guinea pigs is combined with the injection of either adrenalin or pilocarpine[185, 186, 187]. Friedgood, Bevin and Uotila[186] have suggested that the pilocarpine may act through the adrenal medulla and that the adrenalin renders the thyroid cells more sensitive to the thyrotropic activity of the adenohypophysial extract. Friedgood and Cannon[1, 8] have demonstrated that the thyrotropic hormone does not affect the thyroid function by way of its cervical sympathetic innervation. As a matter of fact, recent evidence[169] is against the conception that the autonomic innervation of the thyroid gland activates the function of the parenchymal cells directly.

Comparison of Experimental Adenohypophysial Hyperthyroid Syndrome with Exophthalmic Goiter in Man. — Friedgood has demonstrated that the signs, symptoms, clinical course and response to iodin of the experimentally induced adenohypophysial hyperthyroidism are essentially identical with those encountered in human exophthalmic goiter[16, 163]. With the exception of diffuse and

thyroid gland take place coincidentally Within a week or 10 days a remission in the metabolic disturbance develops in spite of, and because of the continued administration of the adenohypophysial extract which contains the thyrotropic hormone The immediate reason appears to be the inactivation of the thyrotropic hormone by the formation of an antibody to its protein content[163 169 184] The basal metabolic rate returns to its normal value within 1 to 3 weeks Sometimes, however the decreasing rate of oxygen consumption overshoots its original mark and descends to a hypothyroid level, probably because the thyroid has been emptied of its normal colloid stores Involution of the parenchymal hypertrophy and hyperplasia and reaccumulation of acinar colloid lag moderately behind the decreasing metabolic rate By the time the basal metabolic rate has reached its normal level however these regressive, histological changes are fairly complete although the reaccumulated colloid is rather poor in iodin About 8 per cent of the guinea pigs studied were resistant to the thyrotropic effects of the extract and revealed a highly curtailed initial increase in the rate of metabolism and a strong tendency toward an early remission[163 164] Occasionally a brief transitory secondary rise in the rate of metabolism occurred after such an abortive response On the contrary there are other guinea pigs even less in number which display only a negligible resistance to the extract, and after a rapid initial increase in the rate of oxygen consumption suffer several marked exacerbations of their hyperthyroidism Sex is one of the factors that plays a role in the variable response which the thyrotropic hormone elicits This is significant in view of its similar importance in the clinical syndrome of exophthalmic goiter Although not an invariable occurrence the metabolic disturbance is more intense and of longer duration in the female than in the male guinea pig[169 170]

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nodular lymphoid hyperplasia which are absent in the thyroids of experimental *adenohypophysial hyperthyroidism the gland is identical in every respect with* that of exophthalmic goiter in man The effect of iodin on the thyroid altered histologically by an adenohypophysial extract and upon the course of experimental adenohypophysial hyperthyroidism is exactly comparable in all known *respects to that of its action in exophthalmic goiter* [81, 1] *The response of* the experimental hyperthyroid syndrome to a given dose of iodin ranges from one which is barely recognizable to one which completely obliterates the hyperthyroid state Within the limits studied larger doses of iodin were more effective than smaller doses in preventing or partially interfering with the expected cycle of hyperthyroidism [67] As in exophthalmic goiter an inadequate dosage of iodin occasionally induced an exacerbation of the hyperthyroid state whereas a large dose sometimes was followed by a decrease in metabolic rate to hypothyroid levels [67, 1, 8, 170]

It is recognized generally that in most cases of exophthalmic goiter treated with iodin there is an optimal period during which the basal metabolic rate decreases to its lowest level and after which it increases in spite of the continued administration of the drug This has led to a widespread practice of restricting the use of iodids to the preoperative preparation for thyroidectomy during the second or third week of therapy Escape from the depressant influence of iodin also occurs in experimental adenohypophysial hyperthyroidism Means and Lerman[19] believe that the secondary increase in metabolism in the clinical syndrome is not dependent upon refractoriness to iodin but should be attributed to an increase in the intensity of hyperthyroidism which masks the effect of the iodin The observed effect of iodin on the course of experimental adenohypophysial hyperthyroidism suggests another possible explanation for this phenomenon This evidence indicates that the action of iodin is short lived in the experimental syndrome and it has been established by other adequate metabolic and cytological data that the effect of iodin on the thyroid is transitory or in other words that the thyroid becomes refractory to its action[169, 181, 1, 193, 94, 195, 196, 187, 188, 1, 9] *Since the response to iodin in the experimental and clinical syndromes is identical in every other way* it is probable that the same is true of the post iodin or refractory phenomena In this connection it should be emphasized that the administration of iodin is attended not only by a temporary depressant *effect upon the rate of secretion of the thyroid hormone but also by the rapid* restoration to the thyroid of a previously depleted store of hormone This unusual accumulation of colloid makes it possible for the thyroid which is in a hypersecretory state to deliver increasing amounts of thyroid hormone to the circulation as soon as the depressant effects of iodin wear off This accounts satisfactorily for the apparent increase in intensity of hyperthyroidism which

Means has noted In accord with this hypothesis is the observation that the administration of iodin sometimes causes an exacerbation instead of a depression of the hyperthyroidism both in the experimental and the clinical syndrome Analysis of the experimental data indicates that this occurs whenever the dosage of iodin is too small to be effective[169 1 0] A similar response has been noted infrequently as a result of what appears to be an individual idiosyncrasy of the animal In either of such circumstances the metabolic forces, which promote hypersecretion are greater than those which inhibit it Consequently replenishment of the depleted colloid adds fuel to the fire of hyperthyroidism

The point at which iodin is administered in relation to the cycle of hyperthyroidism in the experimental syndrome influences to some extent the intensity of its effect If iodin is withheld until the 'spontaneous' remission begins, it induces a rapid decrease in the basal metabolic rate which persists for some time at a hypothyroid level[1 1] This finding may be of practical importance in directing the therapy of those patients with exophthalmic goiter, in whom the administration of iodin occasionally results in an unusually prolonged remission at hypothyroid levels On the basis of these experimental results the author suggested[169 1] that such patients might be entering upon a favorable phase of the malady and consequently would be more suitable for continued treatment with iodin than for thyroidectomy This has been confirmed by Means and Hertz[00]

Cytology in Relation to Secretion

The cytological changes, which occur in the hypophysis in both types of chromophiles after thyroidectomy are not unlike those following gonadectomy[6 01 0] There is a marked increase in the number of basophiles[6 39 0 0 04], which occurs within a week after thyroidectomy subsequent to which vacuolation becomes apparent The onset of vacuolation is earlier and its speed and degree of development are much more pronounced after thyroidectomy than following castration In the early stages the cytological appearance of these vacuolated basophiles is remarkably similar to the typical castration cell[r 01] The older vacuolated thyroidectomy' basophiles become much larger and more irregular in outline than the 'castration cell

Experimental thyroidectomy in the rat and rabbit results in a marked decrease in the acidophiles of the hypophysis[6 01 3 04 0 06] Identical observations have been reported in clinical myxedema[0 0 08 09 10] The decreased proportion of acidophiles induced by thyroidectomy apparently is more pronounced than that which occurs following castration The marked loss of acidophiles is due to a permanent depletion of their specific granulation which reaches its peak after about 6 weeks At this time there may be no acidophiles,

all of the latter having returned to an inactive chromophobic state There is a *concomitant regression in the Golgi apparatus which retains its characteristic* acidophilic type[91] The administration of thyroid substance either parenterally or orally, to the thyroidectomized rat or rabbit specifically restores the acidophiles to their normal numbers[6, 96]

The parenteral or oral administration of thyroid to normal adult male rats results in an increase in the number and vacuolation of the basophiles[11] Curiously enough this vacuolation is identical with that found after castration or thyroidectomy The hyperthyroid rats also develop a marked acidophilia These cells are actively secretory the Golgi apparatus and mitochondria are hypertrophied, the cells grow larger and their granules which show a marked affinity for the dye are being discharged constantly

Although similar cytological changes occur in the basophiles after gonadectomy and thyroidectomy the hypophysis exhibits an increased gonad stimulating power after the former but not the latter *This suggests either that there is no* correlation between cytology and function or that what appear to be identical cytological changes represent closely allied biochemical processes which are engaged in the manufacture of different tropic hormones

THE OPHTHALMOTROPIC ACTIVITY OF THE ADENOHYPOPHYSIS AND ITS BEARING ON THE CLINICAL SYNDROME OF EXOPHTHALMIC GOITER

Introduction

The pathogenesis of exophthalmos in exophthalmic goiter has been the subject of considerable controversial speculation for a period of many years This situation may be attributed to the fact that opportunities for the experimental study of exophthalmos in the human are subject to obvious limitations Recent advances have made it possible however to induce exophthalmos experimentally in mammals and the results of such investigations have been found to be applicable to the problem in man A review of the clinically important aspects of this situation was undertaken by this writer in a previous communication[184] The present discussion is concerned only with the role of the adenohypophysis in the experimental production of exophthalmos and with the physiological and clinical significance of this relationship

Historical Consideration

In 19 4 Spaul[187, 188] noted that bulging of the eyeballs was one of the earliest manifestations of the metamorphosis induced in normal tadpoles and axolotls by

injections of a crude adenohypophysial extract Schockaert[153] was the first, however to comment specifically on the exophthalmos which results from such treatment The ducks with which he worked developed hyperthyroidism within the first week of the experiment and 14 out of 15 showed exophthalmos on or about the 20th day of injection The exophthalmos vanished promptly during ether anesthesia and disappeared within one or two weeks, if the injections were discontinued The following year[1] Loeb and Friedman issued a brief communication on studies of the guinea pig in confirmation of Schockaert's work They observed the appearance of exophthalmos after 4 to 6 daily injections of an acid extract of the adenohypophysis and found that it disappeared in complete narcosis, malnutrition and death Friedgood[16, 163] noted similar decreases in exophthalmos very early in the experimental period but he reported that the position of the eyeball was not affected appreciably by narcosis or death once the exophthalmos was well established (see Fig 21)

Relation of Thyroid Function to Experimental and Clinical Exophthalmos

Friedgood[163] has made detailed observations on the intensity of exophthalmos in relation to the state of function of the thyroid gland in guinea pigs injected daily for 6 months with a potent chemically crude adenohypophysial extract He found that the hyperthyroidism induced by daily injections of an alkaline adenohypophysial extract lasts about 2 to 3 weeks after which the basal metabolic rate falls to a slightly subnormal level in spite of continued injections of the extract Exophthalmos appeared in 9 out of 30 treated guinea pigs during the height of the hyperthyroidism but it became more marked when the hyperthyroidism declined and was most striking when the basal metabolic rate became abnormally low

It was concluded that a decrease in function of the thyroid favored the development and persistence of the exophthalmos which resulted from daily injections of this adenohypophysial extract As a matter of fact the entire absence of thyroid function makes the action of extracts provoking exophthalmos even more effective because exophthalmos appears more promptly and more frequently in thyroidectomized guinea pigs than in normal ones[171, 182]

It is agreed generally that exophthalmos in exophthalmic goiter is not due to the hyperthyroidism per se and that exophthalmos cannot be induced by the administration of thyroid to a normal animal Moreover it is commonly recognized that exophthalmos is not necessarily present even in severe cases of exophthalmic goiter Exophthalmos frequently may appear for the first time after subtotal thyroidectomy for exophthalmic goiter or, having been present before

operation can become worse afterwards Ruedemann[1] who has made an extensive study of exophthalmos in post operative exophthalmic goiter, attributes its development to a deficient thyroid secretion which is characterized in most cases by a progressive lowering of the basal metabolic rate In a case of this sort he found edema of the upper and lower eyelids and a classical picture of post operative myxedema

That myxedema can in some circumstances either be responsible for or favor the development of exophthalmos is well known Cley[3] was the first to report that thyroidectomized rabbits might develop myxedema spontaneously and Marine and Rosen[14] have found that thyroidectomized rabbits are much more likely to develop exophthalmos induced by cyanide than are unoperated controls Rabbits are highly sensitive subjects for this experiment but the condition apparently also occurs with some rarity in the myxedema of man (see unpublished data of Friedgood Cattell and Beetham[1])

Thomas and Woods[15] studied 15 cases of progressive exophthalmos following thyroidectomy in man In those orbits which were explored they found Tenon s capsule displaced anteriorly by edematous hypertrophied retrobulbar tissue On the basis of their experience these investigators conclude that exophthalmos may develop in the absence of clinical hyperthyroidism but they do not consider that hypothyroidism is an essential predisposing factor In an effort to justify their belief that thyroid insufficiency is not an important factor in the pathogenesis of post thyroidectomy exophthalmos they point out that total ablation of the thyroid in the treatment of cardiac failure does not induce exophthalmos

They overlooked the fact, however that the fundamental pathological physiology prior to operation differs completely in both instances In the case of the cardiacs the function of the endocrines prior to thyroidectomy has been essentially unaffected in that of the goiter patients there already existed a stimulus which is potentially or actually productive of exophthalmos It is true that thyroidectomy in exophthalmic goiter generally affects this stimulus favorably by interrupting whatever it is that initiates the entire goiter syndrome but in the light of other well known evidence it appears likely that in a small percentage of cases a serious form of exophthalmos may be precipitated by this operation The protective action of an intact thyroid function against the development of exophthalmos is substantiated further by Soley s experiments[16] He found that there was an increase in prominence of the eyes of a majority of the patients with toxic diffuse or toxic nodular goiter following subtotal ablation of the thyroid although clinically the eyes appeared less prominent The apparent improvement of the exophthalmos was due mainly to disappearance of the staring expression which results from retraction of the upper lids

mos persisted unabated The changes in the orbit apparently were reversible early in this syndrome but became irreversible eventually Aird[19] who confirmed and extended these observations, found that the pathological anatomy of the orbital tissues and extraocular muscles in the irreversible phase of the guinea pig s exophthalmos is identical with that which Naffziger[20, 21] and others had described for the orbital contents in patients with post operative malignant exophthalmos Smelser, who also has confirmed the author s observations of chronic adenohypophysial exophthalmos, investigated the retrobulbar tissue changes responsible for the proptosis His pathological studies showed that the same retrobulbar tissue changes occurred in the exophthalmos of man and of thyroidectomized guinea pigs injected with an adenohypophysial extract The exophthalmos was due to increased amounts of orbital tissue, such as fat, connective tissue and muscles and there was a great deal of edema of these retrobulbar tissues

Less lymphocytic infiltration and involvement of the extraocular muscles were found in guinea pigs than in man Paulson[4], who studied this problem also, was impressed with the marked edema which he found in the extraocular muscles retrobulbar fat and loose connective tissue This evidence as a whole links an important aspect of Graves' disease securely to its counterpart in the experimental animal syndrome

One may assume for the present until further evidence is brought to bear upon the problem, that ordinary exophthalmos in exophthalmic goiter and so called malignant exophthalmos represent reversible and irreversible phases, respectively, of this phenomenon In such circumstances a single stimulus could be responsible for the development of both types of exophthalmos the so called malignant type would occur clinically only when certain conditions favored the onset of the irreversible phase The intensity of the stimulus producing exophthalmos must be one of these conditioning factors, and another is apparently a decrease in function of the thyroid gland There are probably a number of other factors which play an important role in this connection The sex of the individual and the state of function of the gonads probably are among those which significantly influence the stimulus producing exophthalmos

Hertz Williams and Means[18] have pointed out that malignant post operative exophthalmos is much more common in males than in females Marine[5], who reviewed 52 such cases in the literature up to 1936 found that the group consisted of 31 males, 60 per cent and 21 females 40 per cent respectively It is an interesting coincidence that Marine s experimental studies of methyl cyanide exophthalmos in rabbits have yielded a similar correlation between that type of exophthalmos and sexuality of the animal Cyanide exophthalmos develops most frequently in young sexually active, male rabbits and is greatly amelio

rated or prevented from developing by performing gonadectomy [14]

Judging from the clinical course of both types of exophthalmo reversible and irreversible the changes in the orbital tissues which are responsible for protrusion of the eyeballs must be in part of a labile nature The prominence of proptosis in acute exophthalmic goiter may fluctuate quite readily from time to time and exophthalmos sometimes recedes fairly rapidly in a post thyroidectomy remission Moreover the development of malignant post operative exophthalmos frequently is of strikingly sudden onset and rapid progression There is no acceptable evidence upon which to postulate that the muscles of the orbit take a significant part mechanically in pulling the eyeball forward[1 4] Nor is it conceivable on the basis of this evidence that engorgement of the blood vessels per se could account for this condition although this factor has not been studied exhaustively as yet Careful tudies of the orbital contents of patients dying with acute exophthalmic goiter show surprisingly little Friedenwald [8] found the extraocular muscles of 6 such patients entirely normal and those in a seventh case were slightly enlarged and showed degenerative changes and cellular infiltration On the other hand striking pathological changes have been noted in the extraocular muscles and orbital tissues of patients with post thyroidectomy exophthalmos [0 1 27 8 9 0]

The sum total of these and other observations indicate that three pathological changes are characteristic of so called malignant post thyroidectomy exophthalmos (1) marked enlargement of the extraocular muscles associated with edema lymphocytic infiltration and fragmentation of muscle fiber (2) edema of the orbital fat and connective tissue (3) increase in the amount of fat and retrobulbar connective ti ue which with the exception of the edema appear to be normal histologically

The encroachment of these space-occupying pathological changes on the contents of the non distensible orbital cavity adequately accounts for the progressive and serious nature of such proptosis Available evidence suggests that this is the human counterpart of the irreversible phase of exophthalmos which was observed in the guinea pig syndrome Analysis of the foregoing pathology discloses that only one of the three changes mentioned could possibly be reversible viz the edematous condition of the orbital tissues Can it be that a disturbance in water balance leading to edema of the orbital tissues is the immediate cause of exophthalmos in acute exophthalmic goiter? This would account for the essentially negative post mortem findings in the orbits of many such patients and fits in with the edema or puffiness of the eyelids which is seen not uncommonly in exophthalmic goiter (Figs 2 and 23) Whether or not the irreversible pathological changes are merely secondary to damage done by edematous infiltration of the retrobulbar tissues is a problem for further study This is not quite likely since the marked

increase in the fat and connective tissue content of the orbit is also in need of explanation

The effect of the ophthalmotropic substance, which produces exophthalmos particularly in post operative malignant cases, is especially noteworthy because of its predilection for the orbital tissues, although patients thus afflicted often show



FIG 22 Persistent severe exophthalmos after subtotal thyroidectomy which alleviated clinical syndrome otherwise Note edema of the upper and lower eyelids with only slight widening of the palpebral fissures

evidence of edema elsewhere, e g pitting edema over the tibiae This is apparently not the only substance which acts thus since para phenylenediamin hydrochloride exhibits a similar property and likewise induces exophthalmos the anatomical cause of which is edema of the orbital tissue [31] This chemical, which thus affects dogs and monkeys, also causes increased epiphora chemosis and injection of the conjunctivae findings which closely parallel the eyes signs in malignant, post thyroidectomy exophthalmos

The use of the word ophthalmotropic with reference to this effect of an adenohypophysial extract does not imply that a specific chemical substance having this physiological action is believed to exist as such in the gland The fact that the ophthalmotropic activity of the extract probably is directly or indirectly responsible for the edema of the orbital tissues suggests that it may be tied in



Fig 23 Persistent mild exophthalmos after subtotal thyroidectomy Note marked edema of eyelids particularly the upper The exophthalmos appears to be more prominent than it actually is because of the strikingly widened palpebral fissures Compare with Fig 22 in which the situation is quite the reverse Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

with the important role which the adenohypophysis plays in regulating water metabolism That this may be a generalized disturbance in water metabolism is suggested by two other observations (1) the edema in patients of this type may be particularly impressive in the orbit but it has been observed also in other tissues e g over the tibiae (2) an impaired function of the thyroid gland apparently is a common finding in this type of patient How this contributes to the tendency to develop exophthalmos is unknown but it is well to recall that the thyroid influences water metabolism and may have an essential relation with the adenohypophysis in maintaining a proper water balance

Clinical Application of Experimental Observations on Ophthalmotropic Activity of Adenohypophysial Extracts

The observations which have been presented, indicate that exophthalmic goiter is a syndrome in which either the thyroid or the eyes may become the outstanding problem in therapy It is essential, therefore, to be able to differentiate clinically between these two types of cases, for in the one thyroidectomy is at present usually the treatment of choice, while in the other this operation may precipitate a disastrous ocular complication Our clinical experience still is too limited to speak with assurance of this differential diagnosis, but where so much is at stake in the choice of therapy, one is justified in being guided for the present by certain common sense, clinical criteria and by the experimental laboratory data

Since edema of the orbital tissues probably is an early pathological change in this type of case one should regard with suspicion any preoperative chemosis, lacrimation or puffiness and venous congestion of the eyelids The development of hypothyroidism during iodin therapy or the presence of thyrotropic hormone in the urine likewise should put one on guard, since these findings are associated with an abnormal decrease in thyroid function which undoubtedly is a predisposing factor in the development of ocular complications As a matter of fact a decrease in metabolic rate to hypothyroid levels during iodin therapy may be a contraindication to thyroidectomy even if exophthalmos is not the major consideration Haines [3] and Thompson and his associates [33, 34, 35] have described a group of patients with exophthalmic goiter, in whom the administration of iodin causes a significant fall in basal metabolic rate to what are ordinarily considered moderate hypothyroid levels seldom below minus 20 per cent The latter may occur with or without clinical evidence of hypofunction of the thyroid gland or myxedema The significance of this clinical observation became clear during a study of experimental adenohypophysial hyperthyroidism in guinea pigs treated with iodin[166, 167] and led the author to postulate that patients reacting in this manner to iodids were entering upon a favorable phase or remission of their malady and were more suitable for continued treatment with iodids rather than for thyroidectomy[169, 1 0, 184] Hertz and Means [0] subsequently found this to be a valuable guide in their selection of cases for non surgical treatment Finally one should hesitate to operate on individuals particularly males who have an exophthalmos which is a more striking part of the syndrome than their hyperthyroidism or thyroid enlargement (Fig 24)

The features which have been mentioned already, likewise should be warning signals in the post operative period An increase in exophthalmos, the development of edema or venous congestion of the eyelids and a relatively low basal

metabolic rate especially if associated with an increasing blood cholesterol or the appearance of thyrotropic hormone in the urine, may be significant premonitory findings

The medical treatment of post-operative malignant exophthalmos once it has developed, is notoriously unsatisfactory Dessicated thyroid, either alone or in combination with iodin, has had only meager success in our hands and apparently

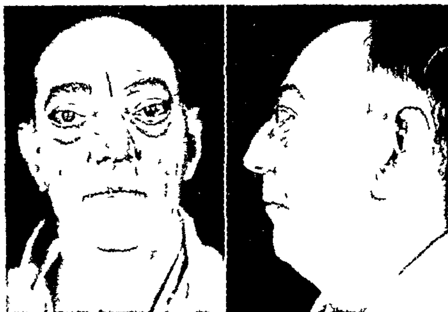


Fig 24 Post thyroidectomy malignant exophthalmos Note extensive edema of upper and lower eyelids chem sis and epiphora Patient treated with success subsequently by x ray therapy of the orbit

this is also the experience of others Presumably the administration of thyroid would be more effective as a preventive than as a therapeutic procedure once this difficulty has developed The administration of large doses of estrogenic hormone in an effort to depress the activity of the adenohypophysis in a case of menopausal hyperthyroidism has met with partial success in one patient (Fig 25) The right eye improved markedly but the increasing chemosis and progressive protrusion of the left eye which was involved more seriously failed to respond satisfactorily X ray therapy to the hypophysis was not tried in this case, because our limited experience with it at the Peter Bent Brigham Hospital has not been encouraging At the suggestion of Dr M C Sosman several advanced cases



FIG 25 Malignant post thyroidectomy exophthalmos which appeared for the first time after operation Right and left upper photographs taken before treatment show extensive exophthalmos chemosis epiphora and edema of eyelids Lower photograph shows results of therapy with estradiol dipropionate thyroid and application of x rays to orbit

in that clinic have been treated by irradiation directly to the orbit Thus far the results have been impressive but the series of cases is too small to warrant further comment The hope of developing an ideal treatment for this condition lies of course, in a thorough understanding of all the major factors which promote its development Until more is known of these, one should avoid thyroidectomy

in those cases which look suspicious preoperatively If one is confronted for one reason or another with the necessity of subjecting to operation a patient who falls into this category it would be a wise precaution to administer dessicated thyroid in addition to iodin preoperatively, in order to prevent the development of at least one condition viz hypothyroidism which is known to affect the eyes of such individuals adversely

The Carbohydrate Regulating Mechanism of the Adenohypophysis

Physiology

Clinical aspects — Clinical disorders of the adenohypophysis not infrequently are associated with disturbances in carbohydrate metabolism In the hyperfunctional phase of acromegaly for instance there may be a decreased tolerance for carbohydrates with hyperglycemia and glycosuria whereas in Simmonds disease and in the late stages of acromegaly the hypofunctional state of the adenohypophysis is characterized in part by chronic hypoglycemia and hypoglycemic crises There are differences likewise in the reaction of such patients to insulin Conditions which are induced experimentally to simulate these clinical syndromes have served admirably in the study of this endocrine phase of carbohydrate metabolism The latter is affected in essentially opposite directions by adenohypophysial deficiency due to hypophysectomy and by injections of adenohypophysial extracts which induce a functional state equivalent to adenohypophysial hyperactivity

Adenohypophysial Deficiency and Carbohydrate Metabolism — Hypophysectomy in the dog results among other thing in hypoglycemia [6, 37] extraordinary sensitivity to insulin interference with gluconeogenesis from protein [1] and in fasting animals a rapid depletion of the glycogen stores of the liver and muscles [1, 4] The effect of hypophysial ablation on carbohydrate metabolism has been illustrated in still another way by Houssay and Biasotti [1] who noted that the course of diabetes in pancreatectomized toads and dogs is ameliorated markedly by hypophysectomy inasmuch as such animals live longer show less glycosuria and have only infrequent acetonuria as compared with pancreatectomized controls The decrease in the rate of glucose absorption from the intestinal tract which is characteristic of the hypophysectomized rat [43, 4] has been traced to the secondary hypothyroidism which occurs after hypophysial ablation

Excessive Adenohypophysial Secretion and Carbohydrate Metabolism — A functional state exactly opposite to that observed after hypophysectomy can be created by the administration to normal animals of a chemically crude adenohy

pophysial extract The extent of the effect of such extracts on carbohydrate metabolism and the direction which it takes often are determined by species susceptibility and the state of nutrition of the experimental animals Such extracts exhibit diabetogenic glycostatic glycotropic and ketogenic metabolic effects

THE DIABETOGENIC EFFECT — Glycosuria and hyperglycemia result from injections of such adenohypophysial extracts into animals on a normal diet[4, 47, 48] and a well established diabetic condition supervenes, if these injections are administered to susceptible animals, such as the dog over a prolonged period of time This diabetogenic action is less marked in other species, but the inability of the organism to utilize carbohydrates properly during injection of such extracts can be detected by a depression in the respiratory quotient and by characteristic alterations in the glucose tolerance curve[49]

THE GLYCOSTATIC EFFECT — Adenohypophysial extracts, which induce hyperglycemia in fed animals particularly dogs fed carbohydrates, are likely also to bring about an increased accumulation of muscle and liver glycogen This glycostatic effect of the extract quite obviously is the reverse of that which results from hypophysectomy In normal fasted rats however the injection of such extracts reduces protein catabolism which in turn induces hypoglycemia, because the amino acids are the only source of glucose in such circumstances[50]

THE GLYCOTROPIC EFFECT — By virtue of its glycotropic activity an adenohypophysial extract may either abolish the hypoglycemic effects of insulin in normal animals or at least increase resistance to the insulin effect This functional state is the opposite of that which follows hypophysectomy, since the latter renders an animal extremely sensitive to insulin

THE KETOGENIC EFFECT — In fasted susceptible animals adenohypophysial extracts generally produce a condition, which commonly complicates the course of diabetes mellitus in man viz an increased rate of fat catabolism with acetonemia and acetonuria[1, 5, 3, 4] Long[4] points out that this increase in fat catabolism probably compensates for the decrease in protein catabolism which results from treatment with the extract The latter implies that the organism must shift to some other foodstuff to replace the calories lost by the reduction in the proportion of protein in the metabolic mixture

EVIDENCE BEARING ON THE EXISTENCE OF A PANCREATOTROPIC HORMONE

General Considerations — There is considerable discussion in the literature concerning the evidence for and against an adenohypophysial pancreatotropic hormone Claims for the existence of such an entity are based principally on reports that the administration to animals of relatively crude adenohypophysial extracts induces an hypertrophy of the islands of Langerhans an increase in the

insulin content of the pancreas and a decrease in the blood sugar level in certain circumstances The available evidence on these points however is not clear cut possibly because of species differences and variations in the experimental conditions under which the extract is administered It must be emphasized moreover that the production of insulin and the oxidation and utilization of carbohydrates are only indirectly and probably not directly dependent on endocrine factors Thus the tissue demands of the organism expressed through the blood sugar level are thought to be the factors that regulate the production and supply of insulin This is not to deny that the endocrine glands play an important role in the acceleration or inhibition of certain phases of carbohydrate metabolism In this connection Long points out that although the absence of insulin leads to interference with the utilization of carbohydrates removal of the hypophysis or adrenal cortex restores to some degree the ability of the organism to oxidize carbohydrate foodstuff

Adenohypophysial Deficiency in Relation to Pancreatic Function and Morphology — Ablation of the adenohypophysis is followed ordinarily by atrophy and other evidence of hypofunction in the case of all target endocrine glands whose activity is controlled by an adenohypophysial tropic hormone Adenohypophysectomized animals however do not exhibit signs of insulin deficiency As was indicated above they actually show a tendency to utilize carbohydrates to an extraordinary degree Furthermore there is no clear-cut agreement on the morphological changes induced in the pancreas by hypophysectomy Koster [a] who found atrophy of the pancreas in the hypophysectomized dog suggested that the hypophysis might be instrumental in the maintenance of pancreatic function whereas von Bakay [b] reported that the islands of Langerhans were increased in size and number 2 to 6 months after hypophysectomy in the dog Perhaps the time factor is an important consideration in this question

Excessive Adenohypophysial Secretion in Relation to Pancreatic Morphology and Function — Anselmino and Hoffman [c] found that their adenohypophysial extracts which were reported to be free of thyrotropic and gonadotropic effects induced hypertrophy and hyperplasia of the pancreatic islets The decreased blood sugar level of their dogs treated with this extract suggested that the hyperplastic islet tissue also showed increased functional activity Richardson and Young likewise have noted islet hypertrophy in rats treated with crude adenohypophysial extracts which were known to produce glycosuria and permanent diabetes in dogs Richardson and Young [58] found furthermore that extracts of known diabetogenic properties caused hypertrophy and hyperplasia of the islet cells initially only to induce subsequent hydropic and hyalin degeneration of these structures in dogs rendered permanently diabetic by such injections

There is apparently a marked species difference in the functional response of

islet cells to the administration of an adenohypophysial extract which influences carbohydrate metabolism Such treatment in the dog causes a rapid and considerable decrease in the insulin content of the pancreas [60], whereas the same type of extract increases the insulin content of the rat s pancreas both in the intact [61] and the hypophysectomized animal [6] [63] Certain evidence suggests that chemically crude extracts of the adenohypophysis can be fractionated into two parts, one of which increases, while the other decreases the insulin content of the rat's pancreas [64]

Experimental studies of the insulin content of the hypophysectomized rat s pancreas have yielded essentially negative results Haist [6] has demonstrated that hypophysectomy only slightly reduces the insulin content of the rat s pancreas, and that the feeding of fat causes a further decrease just as it does in the normal rat which has not been operated upon The reduced insulin content of rats fed a fat diet can be restored to normal both in hypophysectomized rats and those not operated upon by returning them to a mixed diet Evidently the insulin content of the islet tissue not only is relatively unaffected by adenohypophysectomy but also is able to respond in the usual fashion to alterations in the demands of tissue metabolism for insulin

Nitrogen Retention in Relation to Adenohypophysial pancreatic Function — Mirsky [66] has suggested that the nitrogen retaining effect of adenohypophysial extracts is due to stimulation of the pancreatic islets by a pancreatotropic hormone The resulting increased supply of insulin was thought by him to decrease deamination in the liver and to increase protein synthesis in the muscles Young [67] who likewise supports the thesis of a pancreatotropic hormone, found that puppies, in contrast to dogs do not develop glycosuria when treated with an adenohypophysial extract unless it is administered over a prolonged period of months

Such puppies treated with extract show nitrogen retention and a gain in weight which occurs in association with hypertrophy and hyperplasia of the islet tissue Presumably the latter secretes enough insulin to neutralize, at least temporarily the diabetogenic activity of the extract Young suggests that the adenohypophysis contains at least two principles affecting carbohydrates i e a pancreatotropic hormone that stimuates insulin secretion, which in turn increases nitrogen retention and causes a gain in weight and a diabetogenic hormone which either suppresses carbohydrate oxidation or increases carbohydrate formation Gaebler and Gailbraith [69] have pointed out that an increased insulin output may not be the immediate and only cause of the observed nitrogen retention after injections of an adenohypophysial extract although they concede that the presence of insulin may be an essential prerequisite for it

Relation of Adrenocortical Function to Adrenohypophysial Regulation of Carbohydrate Metabolism

A discussion of adenohypophysial function in relation to carbohydrate metabolism scarcely would be complete without reference to the adrenal cortex because a large part of the diabetogenic activity of the adenohypophysis is mediated by the latter The evidence on this point is unequivocal The diabetes of partially depancreatized rats is aggravated by adrenocortical hormones of the corticosterone type just as it is by adenohypophysial extracts and total pancreatic diabetes is ameliorated to the same degree by adrenalectomy and hypophysectomy [6] Furthermore both hypophysectomy and adrenalectomy decrease significantly the rate of protein catabolism and gluconeogenesis under the stress of fasting exposure to cold or low oxygen tension pyrogenic agents and phloridzin or pancreatic diabetes all of which normally would increase the rate of protein metabolism and gluconeogenesis [4] The decreased rate of protein catabolism and gluconeogenesis resulting from hypophysectomy may be attributed to hypofunction of the adrenal cortex because the administration of adrenocorticotropic hormones completely obviates the profound hypoglycemia and depleted carbohydrate stores which would occur otherwise in the fasting hypophysectomized animal [4] Another metabolic defect common to hypophysectomized and adrenalectomized animals is their extraordinary sensitivity to insulin It is interesting furthermore that the anti insulin effect of adenohypophysial extracts the so called glycotropic activity is paralleled by an identical action of cortical extracts adrenal steroids of the corticosterone type and the adrenocorticotropic hormone [3] Because of the latter Jensen and Grattan have suggested that the adenohypophysial glycotropic effect is obtained indirectly through hypersecretion of the corticosteroids which in turn increase the available carbohydrate stores of the liver and the blood sugar level [69]

Although a significant portion of the diabetogenic activity of the adenohypophysis is mediated by the adrenal cortex there are also some important differences which indicate that not all of the disturbances in carbohydrate metabolism after hypophysectomy can be assigned to adrenocortical hypofunction One such difference between these two types of endocrine deficiency is illustrated by the alterations in carbohydrate metabolism which occur with fasting after hypophysectomy and after adrenalectomy Fasting induces hypoglycemia after both operations but the decrease in blood sugar level is more profound and develops more rapidly after hypophysectomy than after adrenalectomy Moreover the glycogen content of the liver is reduced markedly after either operation but the adrenalectomized animals maintain their muscle glycogen stores fairly well whereas they are depleted rapidly in hypophysectomized animals The latter

taken in conjunction with the excessive rate of carbohydrate utilization of hypophysectomized animals constitutes a very significant difference between the two types of endocrine deficiency according to Long[4] These two types of glandular deficiences differ also in the rate of their immediate post operative, nitrogen excretion The nitrogen output proceeds at a greatly increased pace subsequent to hypophysectomy in rats, whereas it is much smaller than normal after adrenalectomy[4]

The adrenal cortex also initiates some direct effects of its own on carbohydrate metabolism Ingle has induced an extensive glycosuria in a normal rat injected daily with 11 dehydro 17 hydroxycorticosterone[7] Injections of such hormones do not alter the muscle glycogen of fasting animals, but they do increase markedly the glycogen content of the liver and raise the blood sugar level moderately Long[4] believes that the corticosterone type of hormone stimulates glucogenesis from protein directly and indirectly induces an increase in the rate of protein catabolism Long Katzin and Fry[71] have reported that this increased rate of protein metabolism which occurs concomitantly with the increase in carbohydrate stores of the organism is sufficient in magnitude to account for the extra carbohydrate found

The Adrenocorticotropic Hormone

Chemistry

Collip, Anderson and Thompson were the first to report the preparation of an adrenocorticotropic hormone by methods[7 3] which have not yielded successful results in other laboratories[1 5 74] The reasons for this failure to confirm Collip s work have been discussed at some length in a timely critique by White[1 5] Highly purified preparations of this hormone became available in 1933, and more recently these have been prepared without appreciable growth, gonadotropic or thyrotropic effects[1 74 75 6 77 8 9] Two groups of investigators, one at Yale[78 279], the other at California[77 80], have studied this problem independently with hog and sheep hypophyses respectively The adrenocorticotropic hormone content of the hog hypophysis is much higher than that of any other species examined[6 77 8] Although the methods of preparation used in the two laboratories are distinctly different one employing essentially salt fractionation[7] and the other isoelectric precipitation[279] it is clear that they have both succeeded in isolating the same substance from their two sources of supply Li, Simpson and Evans[280] have reported that their final product behaves as a single homogenous protein in electrophoretic and solubility studies Sedimentation and diffusion measurements also indicate that this preparation is homogenous or very nearly so Biological tests show that their adrenocorticotropic hormone is free of the other

adenohypophysial hormones The molecular weight was found to be approximately 20 000 and the isoelectric point about pH 4 7 The hormone is remarkably stable at 100 C in buffer at pH 7 5 and in 0 1 molar hydrochloric acid solution but not in 0 1 molar sodium hydroxide solution Although its biological activity is destroyed by trichloracetic acid and by tryptic digestion pepsin leaves it relatively unchanged

The purified adrenocorticotropic hormone prepared by the Yale group [5, 79] gives the usual protein color reaction The Molisch test is negative Although the labile sulfur test is positive the nitroprusside reaction for free sulfhydryl groups is negative The hormone is precipitated easily from dilute solution by 20 per cent sulfosalicylic acid by 20 per cent trichloracetic acid and by 5 per cent lead acetate solution The initial protein boundary was found to migrate as a single component at all pH values studied in the Tiselius apparatus i e pH 3 26 4 13 6 37 and 7 95 In accord with Li Simpson and Evans it is reported by White[123] that the molecular weight of the adrenocorticotropic hormone is 20 000 and the isoelectric point 4 7 to 4 8 Having subjected the purified adrenocorticotropic hormone to elemental analysis both groups of investigators report essentially the same percentage of carbon hydrogen nitrogen and sulfur

Physiology

Evidence for the existence of an adrenocorticotropic hormone like that for all other physiologically active substances of the adenohypophysis has been obtained from two general sources viz the condition of the adrenal gland after hypophysectomy and after the injection into animals of chemically crude and highly purified adenohypophysial extracts

Histological Changes in Adrenal Cortex Resulting from Hypophysectomy — It is accepted generally that hypophysectomy is followed by marked atrophy of the adrenal cortex in all species which have been examined [4, 3, 64, 8, 66, 7, 8, 6] and that compensatory adrenal hypertrophy which ordinarily follows unilateral adrenalectomy does not occur in the hypophysectomized animal [91, 8, 4, 5, 4] The histological changes in the adrenals of hypophysectomized rats and dogs have been investigated carefully [87] The medulla appears normal The cells of all three zones of the cortex are smaller but are not decreased in number Fat deposits are limited to a central zone The earliest changes appear in the reticular zone and in the inner part of the fascicular zone Here the cells become progressively smaller until these regions no longer possess a normal, cord like arrangement of cells Thereafter the entire cortex becomes involved similarly Evidence from clinical sources also amply confirms the dependence of the adrenal cortex upon intact adenohypophysial function Extensive atrophy of the

adrenal cortex is associated with adenohypophysial pathology and hypofunction[98, 99] In hypophysial dwarfism the adrenals are very small and show hypoplastic changes in the cortical layers[00, 301, 60, 303] In Simmonds' cachexia the adrenal glands are small although frequently histologically normal[304, 30, 306, 307]

Histological Changes in Adrenal Cortex Induced by Adenohypophysial Extracts —In 1929 Putnam Benedict and Teel[308] found cortical adenomas in the adrenals of dogs, which were injected over a relatively long interval with an alkaline extract of the adenohypophysis In 1932 Evans and associates[309] observed that the injection of growth promoting extracts caused cellular hypertrophy of the fasciculate zone with some increase in the amount of cortical lipoids In 1933 Emery and Atwell[6], Friedgood[16, 163, 310] and Houssay and associates[83] reported independently that the daily injection of partially purified adenohypophysial extracts resulted in marked hypertrophy and hyperplasia of the adrenal cortex in the rat, guinea pig and dog This was confirmed abundantly by numerous subsequent observers, some of whom demonstrated also that suitable extracts or implants of the adenohypophysis restored the atrophied adrenals of hypophysectomized animals to their preoperative normal state Emery and Atwell concluded that the hyperplastic changes in animals treated with adenohypophysial extract involved both reticulate and fasciculate zones[28]

Early studies seemed to show that this adrenocorticotropic effect of the adenohypophysis was mediated through the thyroid gland[311, 31, 313, 314, 315] In a statistical analysis of his data Friedgood[310] demonstrated, however, that only a portion of the adrenocortical hypertrophy could be attributed to the thyroid hormone He based this conclusion on the fact that the significant correlation between adrenal weights and intensity of hyperthyroidism accounted for merely a part of the adrenocorticotropic effect of the adenohypophysial extract This was confirmed subsequently by others who found that adrenal hypertrophy occurs in thyroidectomized animals treated with adenohypophysial extract[310, 317, 18]

Functional Significance of Histological Alterations —The functional significance of these histological changes is far from being understood, but a good beginning has been made in its investigation Among the physiological effects, which have been observed after the administration of the adrenocorticotropic hormone are alterations in the cholesterol and ascorbic acid content of the adrenal cortex, changes in the structure and function of lymphoid tissue and inhibiting influences on body weight chondrogenesis and osteogenesis The relation of this hormone to renal hypertension, work performance and carbohydrate metabolism also are being investigated

Cholesterol and Ascorbic Acid Content of Adrenal Gland —In view of the fact that the active principles of the adrenal cortex are steroids, the cholesterol content of the gland has been investigated with the thought that variations in its

concentration might reflect changes in the synthesis and secretion of the steroid hormones Such studies have disclosed that a single dose of adrenocorticotropic *hormone diminishes the cholesterol content of the adrenal cortex of the immature* white rat by one half to two thirds of its normal level within 3 hours whereas repeated daily injections over a period of 3 days results in an increase of the cholesterol content above the normal control level[319 3 0 3 1] The initial maximum depletion of cholesterol which takes place 3 hours after the administration of hormone is followed by recovery within 12 to 24 hours Sayers Sayers Lewis and Long[3] have postulated that the more rapid depletion and recovery in the ascorbic acid content of the adrenal cortex after similar hormone therapy is related either *to the synthesis of adrenocortical hormone or its release from the adrenal gland*

Influence on Structure and Function of Lymphoid Tissue and Spleen — In 1936 Perla[2] [3 3] and Friedgood[1] called attention independently to the possi*ble significance of certain relations between the adenohypophysis and the spleen* The author[810] reported that a statistically significant increase in the weight of the spleen of guinea pigs resulted from the daily injection of an alkaline extract of the pars distalis of the adenohypophysis He observed furthermore that the splenomegaly occurred in association with marked hypertrophy of the adrenal cortex A limited cycle of hyperthyroidism due to hypertrophy and hyperplasia of the thyroid parenchyma represented another coincidental change induced by the adenohypophysial extract The mean weight of the spleens removed from normal *females was found to be significantly greater than that of the spleens from normal* males In this connection it may be of interest to point out that the female hypophysis is heavier on the average that that of the male in all human races which have been studied The pioneer and important investigations of Perla[3] [4] extended and interpreted these observations in the relation of the spleen and adenohypophysis from an immunological viewpoint His data proved that hypophysectomy is followed by a decrease in natural resistance to various toxins and poisons and to spontaneous and induced bacterial and protozoal infections be*cause of atrophy of the spleen and lymphoid tissue of the body* Perla demonstrated moreover that the adenohypophysis affects the animal s natural resistance because of the controlling influence of the adrenocorticotropic hormone over the physiological activity *of the adrenal cortex and the spleen and lymphoid* tissues The more recent investigations of Dougherty White and Chase[3] [3 4] [4 4] have confirmed and extended the foregoing observations with a pure adrenocorticotropic hormone They have found that the adrenocorticotropic hormone and the adrenocortical steroids are concerned with the mechanism of antibody *formation from lymphocytes* It is proposed to discuss certain aspects of this immunological problem since it is germaine to any consideration of adenohypophysial function

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Cholesterol and Ascorbic Acid Content of Adrenal Gland —In view of the fact that the active principles of the adrenal cortex are steroids, the cholesterol content of the gland has been investigated with the thought that variations in its

in antibody titer in the serum was observed to parallel the activity of the lymphoid cells of the Malpighian bodies of the spleen.

This circumstantial evidence was reinforced conclusively by the observations of McMaster and Hudack [3] who showed that antibodies may be formed in lymph nodes. *When they injected two different antigens into a mouse, one into each* ear, the corresponding antibody appeared first in the ipsilateral lymph node. Ehrich and Harris [3] demonstrated subsequently that the cellular response during antibody formation in such lymph nodes is lymphocytic essentially. Further observations revealed that the injection of antigens into the pad of the hind foot of a rabbit was followed within 2 to 4 days by the appearance of antibodies in the lymph draining the corresponding popliteal lymph node. The antibody titer was *higher in the lymph of the efferent vessel by as much as 100 times that found in* the lymph of the afferent vessel. The production of antibody in the popliteal lymph node was preceded by and associated with a four fold increase in the output of lymphocytes *in the efferent lymph. At the same time the hyperplasia of* the lymphatic tissue within the lymph node resulted in an increase of 0.2 gm to 1.0 gm in the weight of the latter. In a more recent communication Harris, Grimm, Mertens and Ehrich [3] reported that during antibody formation in the *popliteal lymph node of rabbits the lymphocytes in the efferent lymph vessels* contain antibodies in a much higher concentration than the surrounding lymph. Ehrich and Harris believe that the evidence [3, 34, 3] is entirely against the possibility *that the lymphocyte either absorbs or adsorbs these antibodies; it favors* the lymphocytic theory of antibody formation. Many clinical and patholgical observations support this viewpoint [33, 338, 35].

The mechanism of antibody formation, like all other physiological processes, is subject to regulation and control under normal circumstances. The recent investigations by Dougherty, White and Chase [3, 4, 3, 3] have been instrumental in disclosing one of the ways in which this functional adjustment may be accomplished. *Moreover, their studies give experimental support to the clinical belief* that the adenohypophysis has something to do with the regulation of the number of circulating leucocytes and erythrocytes. They found that the administration *to mice and rats of pure adrenocorticotropic hormone resulted in a statistically* significant decrease in the total weight of the lymphoid tissue, exclusive of the spleen, as compared with normal controls. The weights of the inguinal, axillary and mesenteric lymph nodes and the thymus were approximately one half that of the control animals [3, 4, 3, 7]. Further studies with mice and rabbits showed that within 3 hours of its injection this hormone induced degenerative changes in the lymphocytes of the germinal centers of lymph nodes, in the Malpighian follicles of the spleen, *in the cortex of the thymus and in* Peyer's patches. The degenerative changes were characterized by pyknosis and nuclear fragmentation in the

The site of the formation of antibodies was conceded to be the reticuloendothelium until very recently although an increasing body of evidence, which had been largely ignored pointed to the lymphocyte as their source Metschnikoff's reticulo endothelial theory was accorded general acceptance, because it seemed plausible to believe that the cells, which phagocytize and destroy bacteria, should be concerned also with the synthesis of antibodies Of the various arguments, which were advanced in support of this theory, two have been favored especially One of these was based on the observation that the formation of antibodies may be depressed by blocking the reticulo endothelial system with phagocytized substances such as india ink trypan blue, collargol and iron sugar The second of these arguments in favor of Metschnikoff's theory was proposed by Sabin[3 5] She observed that the phagocytosis of a dye protein by a macrophage resulted in the removal of some of the dye from each dye protein aggregate With the removal of the dye the protein particles became invisible and antibodies made their appearance in the serum These phenomena were believed to signify that the protein was converted into a soluble form and assimilated subsequently into the cytoplasm The fact that the cytoplasm of the macrophage was shed coincidentally with the disappearance into the cytoplasm of the dye protein aggregate and the appearance in the serum of antibodies seemed to indicate that the antibody was synthesized within the cytoplasm of the macrophage and extruded subsequently into the circulating blood Ehrich and Harris[3 9], who have reviewed the experimental data critically have come to the conclusion that the interpretation put upon them is open to question They believe, on the contrary, that the known facts are consistent only with the lymphocytic theory of antibody formation

Among the first to contribute to the long chain of evidence in favor of the lymphocytic origin of antibodies was Hektoen[33] who showed that the exposure of rats to x ray caused a decrease in the production of hemolysin coincidentally with a reduction in the number of circulating lymphocytes and in the mass of lymphatic and bone marrow tissue Murphy and Sturm[111] reported subsequently that similar treatment which affected the lymphatic tissue without damaging the bone marrow induced definite decreases in the production of precipitins bacterial agglutinins and protective antibodies in rabbits They noted furthermore that exposure of rabbits to dry heat caused an increase in the activity of the lymphatic tissue which was paralleled by the development of larger quantities of antibodies than untreated animals were capable of producing Ehrich and Voigt[33] added to this evidence by showing that the antibody titer remained low after doses of staphylococcus vaccine which were large enough to stimulate marked proliferation of the reticuloendothelium whereas high titers were elicited with small doses, which did not produce visible proliferation of these cells Furthermore, the rise

mone to the action of the growth hormone was noted also in its effects on the osseus system of normal and hypophysectomized rats[3 344] The proximal epiphyses of the tibiae in normal animals showed retardation in chondrogenesis and osteogenesis but the reduction in width of the epiphyseal cartilage was not so extensive as that which develops after hypophysectomy These bone changes did not occur in the absence of the adrenal glands In hypophysectomized rats highly purified growth hormone induced activation of the cartilage of the proximal epiphyseal regions of the tibiae and formation of the delicate, straight trabeculae of bone was resumed The adrenocorticotropic hormone scarcely affected the inactive condition of the epiphyses on the other hand except that the cartilage cells in the erosion zone were more irregular

Relation to Renal Hypertension Work Performance and Insulin Content of Pancreas — A group of interesting experiments have been reported by Anderson Page Li and Ogden[4] on the restoration of renal hypertension in hypophysectomized rats by the administration of adrenocorticotropic hormone They found that hypophysectomy was followed originally by an average decrease of 44 mm Hg in mean blood pressure The significance of these findings is far reaching inasmuch as they indicate that the adenohypophysis and the adrenal cortex play an important role in the regulation of the renal factors which are responsible for the development of this type of hypertension

Ingle Li and Evans[3 5] have investigated the effect of pure adrenocorticotropic hormone on the work performance of hypophysectomized rats They observed that the hormone induced a marked increase in the amount of work elicited from the gastrocnemius muscle of such animals as compared with the very poor work performance of untreated rats Moreover they noted that repetitive direct faradic stimulation of these muscles resulted in a loss of responsiveness within 12 to 18 hours in the untreated animals whereas the muscle responsiveness lasted 24 to 120 hours in the rats that received the adrenocorticotropic hormone The metabolic importance of these findings is self evident but their ultimate significance still is to be explained

In a previous section of this chapter there appeared a detailed account of the functional relations which exist between the adenohypophysis and the adrenal cortex in so far as carbohydrate metabolism is concerned The availability of a pure adrenocorticotropic hormone with which to experiment has helped to reconcile some of the results of investigators who worked previously with chemically crude adenohypophysial extracts For instance the recent observations of Fraenkel Conrat Herring Simpson and Evans[344] may have a bearing on the question of a pancreatotropic hormone inasmuch as they found that the adrenocorticotropic hormone increased the insulin content of the rat s pancreas by an average of 40 per cent above the normal level The physiological significance

small and medium sized lymphocytes After 3 to 6 hours the lymphoid tissue showed a marked depletion of lymphocytes associated with extensive edema Restoration of the normal structure of lymphoid tissue began about 9 hours after an injection and was detectable for as long as 24 hours subsequently None of these structural changes occurred in adrenalectomized animals which were injected with the same hormone

The loss of lymphocytes from lymphoid tissue was found to be associated with a marked decrease in the number of cells in the circulating blood Single injections of the adrenocorticotropic hormone into mice, rats rabbits and men resulted in a decrease in the total leucocyte count a decrease in the absolute number of lymphocytes and an increase in the absolute number of polymorphonuclear neutrophiles There was also an early initial increase in the amount of hemoglobin, the number of lymphocytes in the circulating blood and probably, the number long as 24 hours afterward The lymphopenia may be considered a specific response to the adrenocorticotropic hormone because it does not occur in adrenalectomized animals treated with this hormone or in normal animals injected with a pure protein Lymphopenia is induced in intact and adrenalectomized animals, however, after injection with extracts of the adrenal cortex, adrenocortical steroids in oil corticosterone or Wintersteiner s compound F Desoxycorticosterone was not found to affect the total number of blood lymphocytes in normal or operated animals On the basis of these studies Dougherty and White[3,7] concluded that the number of lymphocytes in the circulating blood and probably the number of erythrocytes is under the control of the adenohypophysis by way of the adrenal cortex

Coincidentally with the involution of lymphoid tissue and the occurrence of lymphopenia there is a significant increase in the total serum proteins as a result of the administration of adrenocorticotropic hormone[3,5] White and Dougherty[3,5] suggest that a portion of this protein may undergo gluconeogenesis in the liver, another portion apparently augments the globulin fraction of the serum proteins, inasmuch as the antibody titer is increased in such circumstances[3,6] These observations tie in neatly with the array of evidence which was cited above, in favor of the lymphocytic origin of antibodies The inauguration of this metabolic phase of immunology may well be the beginning of a new approach to the clinical handling and therapeutic control of certain types of infection

Inhibiting Effect on Body Weight Chondrogenesis and Osteogenesis — Evans Simpson and Li[340] have demonstrated that the body growth of normal and gonadectomized male rats is inhibited by pure adrenocorticotropic hormone derived from the hypophyses of sheep This inhibitory effect was not observed in rats after adrenalectomy which indicated that the phenomenon was mediated by the adrenal cortex The antagonism of the adrenocorticotropic hor

acidophiles are concerned principally with adrenocortical function were it not for studies which have disclosed that the basophiles are the cells that are affected principally in the adenohypophyses of Addison s disease Kraus [6 5 40 51], who examined 7 cases of Addison s disease with tuberculous lesions of the adrenal and 2 other cases of adrenocortical atrophy with the classical Addisonian symptoms reported a general marked diminution in the number of normal basophiles There was almost complete absence of the basophiles in one instance only a slightly decreased number of basophiles in another and a marked decrease in their number in the remaining cases In only one instance was there sparse granulations of the basophiles in the others the basophiles appeared degenerated with indistinct and irregular cell borders degranulation and pyknotic nuclei The acidophiles also were affected somewhat similarly, viz diminished in number atrophic and with pyknotic nuclei The chromophobes consequently were present in larger than normal numbers although many of those were smaller than normal and had pyknotic nuclei These observations were confirmed subsequently in a statistically significant study by Crooke and Russell[35] of 12 similar cases Berblinger[352 2 4] studied 4 cases of which one showed no change in the adenohypophysis and another disclosed only a slight diminution in the basophile count whereas there was a very marked decrease in the basophiles in the remaining 2 cases He regarded the alterations in basophiles as the characteristic adenohypophysial finding in Addison s disease Terplan and Sanes [55] reported a case of Addison s disease treated with adrenal extract in which the hypophysis showed dilation of the capillaries a decreased number of basophiles and a normal chromophobe and acidophile count although the latter were slightly atrophic The basophiles showed degenerative changes characterized by indistinct cell outlines and small eccentric pyknotic nuclei Harrop Weinstein and Marlow[3 6] have reported a decreased basophile count in association with atrophy of the adrenal cortex Only one case of Addison s disease has been reported in which the basophiles were found to be increased in number and in which there was cytological evidence of a heightened secretory activity of these chromophiles[7]

Whereas there is general accord in the reports on adenohypophysial cytology in Addison s disease the literature dealing with histological changes after experimental adrenalectomy in animals is confusing and contradictory [57 35 2 380] Schumacker and Firor [9] examined the hypophysis of a bilaterally adrenalectomized dog that had been maintained in a state of chronic adrenal insufficiency for 128 days after operation They found conditions strikingly like those reported for Addison s disease viz increased vascularity of the hypophysis and a complete disappearance of the basophiles

In attempting to arrive at an understanding of the effect of adrenalectomy on the adenohypophysis there is one factor peculiar to adrenal function which must

of these experiments still remains to be determined, because an increase in the hormone content of an endocrine gland does not signify necessarily that it is associated with hypersecretion. For example, the thyroglobulin content of the thyroid gland in exophthalmic goiter is at a remarkably low level at a time when its rate of secretion is augmented greatly. Consequently their observations are not incompatible with those of Ingle, who reported that the normal rat reacts to the daily injection of 11-dehydro-17-hydroxycorticosterone with hyperglycemia and glycosuria. This is true particularly, if one assumes with Long that the corticosterone type of hormone stimulates gluconeogenesis from protein directly. The extra carbohydrate formed in this fashion, furthermore, might be protected by the glycotropic or anti-insulin effect, which has been attributed to the adrenocorticotropic hormone by Jensen and Grattan.[illegible] Their findings are in accord with the undue sensitivity to insulin, which characterizes what may be considered the opposite functional state, viz. hypofunction of the adrenal cortex or Addison's disease.

Bio-assay

Simpson, Evans and Li[315] have proposed two methods for the standardization of the adrenocorticotropic hormone. The first unit is based on the daily dose in mgm., which is necessary to maintain the preoperative adrenal weight for 15 days in male rats that were hypophysectomized at 40 days of age. The second unit is determined on female rats that are 26 to 28 days old at the time of hypophysectomy and 40 to 42 days of age when a 4-day period of injection with the test doses of hormone is begun. The unit is based on the total dose in mgm. which induces evidence of adrenal repair, i.e. redistribution of cortical lipid, during the 4 days of administration of the hormone.

Cytology in Relation to Secretion

Current thought on the cytological origin of the adrenocorticotropic hormone has been based chiefly on studies of the adenohypophysis in Addison's disease and in adrenalectomized animals. The bearing on this problem of the cytological changes characteristic of the adenohypophysis of the acromegalic have been ignored essentially. Some of this evidence is contradictory, at least on superficial examination, much of it has not been interpreted physiologically as yet. Hyperplasia of the adrenal cortex is the rule in acromegaly. This disorder is characterized by acidophilic hyperplasia or adenoma with concomitant functional hyperactivity. Although hyperplasia of the adrenal cortex is the usual finding,[98,346,347,348,349] not infrequently adenomata of the cortex also enlarge the adrenals to a marked degree.[2,8,348,349] These findings might suggest that the

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In attempting to arrive at an understanding of the effect of adrenalectomy on the adenohypophysis there is one factor peculiar to adrenal function which must

be taken into consideration. The removal of any endocrine gland induces serious disturbances in all metabolism, but the adrenal differs from all other glands in that its bilateral removal or pathological destruction results in death to the entire organism whose metabolic functions cannot proceed without its secretions. Consequently, the cytological appearance and functional activity of the adenohypophysial chromophiles must be affected in at least two ways by total adrenalectomy. There should be a specific local effect on the cells supplying the tropic hormone or hormones which are concerned with adrenal functions, and a nonspecific general effect on cellular metabolism. The adenohypophysial cells thus share in the serious consequences to the entire organism of the lack of the adrenal secretions. The latter probably accounts for the failure of the adenohypophysis to react to the insult of adrenalectomy by that pattern of response which characteristically occurs after ablation of certain of the other endocrine glands. For example, thyroidectomy[361], gonadectomy[4, 3, 634], and splenectomy[63] result, among other things, in hypertrophy of the adenohypophysis with cytological and physiological evidence of hyperactivity either in the formation and storage or in the formation and secretion of the corresponding tropic principle. The rare instances in which cytological evidence of functional activity has been detected in the adenohypophysis of Addison's disease, probably resulted from abortive attempts at regeneration of the afflicted adrenal cells.

Further evidence bearing on the cytological origin of the adrenocorticotropic hormone has been reported by Koneff[364], who found that its administration to young and adult male rats results in a marked decrease in the size of the adenohypophysial basophiles and in an extensive depletion of their granules. Koneff believed these cytological changes to be indicative of a state of depressed or retarded functional activity. This response to the injection of the adrenocorticotropic hormone is in accord with the general physiological principle that the administration of a hormone is likely to be associated with involution of the cell which produces it in normal circumstances. The atrophic condition of the parenchyma of the thyroid gland which results from the ingestion of thyroglobulin, is encountered more commonly as an example of this principle. In the case of the thyroid gland the atrophy is secondary to a decreased rate of secretion of the adenohypophysial thyrotropic hormone resulting from an overabundance of circulating thyroglobulin. In like manner an overabundance of circulating corticosteroids, which are produced by the adrenal cortex in response to the adrenocorticotropic hormone, result in depression of the functional activity of the adenohypophysial basophiles. Thus a homeostatic mechanism regulates the rate of secretion of the thyrotropic and adrenocorticotropic hormones and others which behave similarly. This mechanism responds sensitively to the concentration in the blood of the hormone secreted by the target gland which has been stimulated

This ingenious manner of regulating the secretion of hormones is particularly effective because it becomes activated by the same physiological process it is supposed to prevent namely hypersecretion of a hormone Endocrine homeo tasis is achieved also through other physiological means at the disposal of the organism among which are the hypothalamus and the central nervous system Further discussion of this phase of the problem is being reserved for another chapter which is devoted to the endocrine functions of the hypothalamus Other a pects of the neurohumoral regulation of secretion have been described in Part V, which is concerned with the neurohypophysis

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PART III

BIOLOGICAL, BIOCHEMICAL, PHYSIOLOGICAL AND GENETIC CONCEPTS OF GROWTH

DEFINITION AND GENERAL CONSIDERATIONS

The inherent tendency to grow is one of the fundamental characteristics of living things When used in a limited clinical sense, growth is a term which signifies an increase in the size of individuals with special reference to their height and weight Growth may be regarded also as a fundamental biological property of the tissues and organs of physiologically young organisms which have not yet attained maturity In this sense growth is the result of hypertrophy and hyperplasia of the cells of a tissue organ or more substantial part of the immature individual A continuation of the growth phenomenon likewise may be characteristic of certain tissues of a physiologically mature organism For example the bone marrow continues to exhibit hematopoietic activity as long as the individual lives, although the bone itself ostensibly ceases to grow with the closure of the epiphyses The products of hematopoiesis, primitive cells of the myelocytic and erythrocytic series go through various recognizable phases of growth before arriving at maturity From a biochemical viewpoint true growth is characterized essentially by an increased rate of protein synthesis and the newly formed protoplasm, which represents the gain in weight is known to be of rather constant composition[1] [4] The chemical characteristics of newly formed protoplasm, like immature tissue include a relatively high content of water, protein and ash and a low content of fat

The chemical composition of the organism differs at various stages of maturity The intrauterine organism is composed of a relatively high proportion of water, 90 per cent whereas the amounts of protein, 5 to 9 per cent, ash and fat, 1 to 2 per cent each are relatively small After birth the proportion of protein which contributes to the gain in weight increases to approximately 15 to 20 per cent while that of water decreases commensurately As the organism grows older, increasing quantities of fat are acquired, and since fat is deposited with relatively small quantities of water, the percentage content of the organism in water decreases still further The amount of stored fat is fairly constant in young animals

but may vary within extremely wide limits among adults protein, on the other hand exhibits a very limited capacity for storage Because the continued acquisition of fat by the mature organism obscures the actual chemical composition of the body tissues during various stages of growth, Moulton[4] has calculated both the composition of the whole animal and the composition of the gain in weight on a fat free basis This analysis has revealed that the proportions of protein and mineral salts increase progressively during intrauterine life and for a brief period after birth Subsequent to this a point is reached after which the proportions of protein mineral salts and water remain remarkably constant although a highly variable amount of fat may be acquired Moulton has termed this constant period the 'age of chemical maturity'

That the chemical composition of protoplasm is in a constant state of dynamic equilibrium may be surmised from the fact that it is undergoing constant synthesis breakdown and resynthesis although its total quantity remains constant in the mature organism[5] The mature individual apparently retains and continues in operation those processes by which protein is formed and incorporated into protoplasm during the rapid growth period of the immature organism In the immature state these chemical processes result in a progressive increase in the bulk of living protoplasm, because protein synthesis is greater than protein catabolism in the mature state these processes are subjected to new forces which equilibrate the anabolic and catabolic phases of protein metabolism Some conception of the precision of this regulatory mechanism in the adult organism may be gleaned from the homeostasis of the blood proteins[6] the constancy of the nitrogenous constituents of the body and the narrow limits within which the chemical and metabolic characteristics of growth operate The growth phenomenon as a whole is under the control of biologically determined regulatory influences which limit the size of the organism or any of its parts to that destined for the species of which it is a member

The Rhythmic Progress of Normal Growth in Children

The rate of growth of normal children is characterized by a wide range of individual variations Although average standard growth curves have been constructed statistically on the basis of the general population one cannot apply them too specifically in individual instances Nevertheless such data have served a useful purpose in that they have drawn attention to the rhythmic pattern in which normal growth takes place The study of an average growth curve discloses faster and slower periods of growth which alternate in a fairly consistent fashion Godin[7] was among the first to point out that the growth of the long bones of the extremities proceeds by alternate periods of activity and repose which succeed each other

with regularity These alternate phases are not timed concurrently for the various long bones, e g the femur remains stationary during the period when the tibia grows and vice versa Godin found furthermore, that the resting period, during which there is no elongation, is utilized for an increase in the weight and thickness of the bone and vice versa Elongation of the long bones and increases in their transverse diameters and weights also were found to occur alternately, not simultaneously Godin concluded that growth prior to puberty is essentially osseous, while during puberty it is muscular Robertson[8] refers to three waves of growth, each of which is characterized by a period of gradual acceleration, then a peak and finally a phase of retardation The first wave occurs in the first year of post natal life the second phase of relatively rapid growth has its peak during the sixth or seventh years at the time of the second dentition, and the third spurt coincides with the onset of puberty The observations of Stratz[9] and Harris[10], like those of Godin indicate that skeletal growth periodically precedes muscular and visceral growth since they write of three " springing up " periods, each of which is followed by a ' filling out ' period The cycles in their curves correspond chronologically with those of Robertson's[8] It is a matter of clinical record that disturbances of growth are most likely to arise during the three main " springing up periods i e during the first year of life, at the time of the second dentition and with the onset of puberty

A study of average normal growth curves discloses that certain variations can be attributed to sex differences The fast growing period in girls starts sooner finishes earlier and is less intensive than in boys Girls grow more steadily until puberty after which they are more likely to slow down, whereas boys often continue to grow rapidly throughout their early adolescent years Longitudinal growth ceases with the advent of sexual maturity because of closure of the epiphyseal junctions

Factors Affecting Growth

It is well established that growth is affected significantly by many extrinsic as well as intrinsic factors Among the former one may include deficiencies of diet disease and abnormalities of environment such as climatic, seasonal and hygienic conditions Of primary importance among the intrinsic factors are heredity and the growth regulating influences of the adenohypophysis, the thyroid, the adrenals the pancreas and the gonads

Diet

Nutritional deficiencies which affect growth most commonly, can be traced to the omission from the diet of certain indispensable vitamins to the inadequate

quality and quantity of the so called essential amino acids or to an insufficient total caloric intake The influence on growth of these various dietary factors may be studied in detail in the writings of Hopkins[1] Mellanby[1] McCollum and Simmonds[14] and Hess and in the reports of the Scottish Board of Health by Orr Leighton and Clark[15 16]

The short stature of the Italian of the Japanese and of certain other foreign nationalities has been attributed generally to hereditary influence but McCollum[13] Manny[7] and Holt[8] have interpreted the situation otherwise Their data and that of others indicate that the optimal somatic growth of these peoples is limited significantly by diets which are inadequate in essential proteins vitamins and minerals Osborne and Mendel[19] have demonstrated what striking variations there are in the value of proteins from different sources in so far as the support of growth is concerned They found also that animals remained stunted in growth for long periods when the protein content of the diet was limited in amount It is of interest from a therapeutic viewpoint that interruption of growth in such circumstances did not signify necessarily that the capacity to grow had been lost because an increase in the amount of protein of the diet caused the rats to resume growth at a predictable normal rate Mendel and Cannon found moreover that the albino rat has a more rapid rate of growth than that claimed to be standard for it by Donaldson in 1912 This change in the growth rate has been attributed not to selective breeding but to the feeding of a more appropriate diet than had been employed hitherto in the experimental study of rats McCollum noted somewhat similar differences in the growth of his experimental rats When the nutrition of these animals fell just below a certain standard there was no recognizable sign of malnutrition but their size diminished from generation to generation The somatic inferiority of successive generations seemed to be the result of injury during the nursing period or might have been due to restricting the young after they were weaned to the same inferior diet as that of the parents The increase in size of Japanese children born in California where they are fed adequately over that of children of the same ages in Japan harmonizes with this viewpoint

Disease

Any extensive interference with nutrition from acute infections or metabolic disease results in limitation of the growth of the skeleton Harris[10] recently has observed that in such circumstances the structure of the bone is altered histologically and roentgenologically by a transverse line of arrested growth Apparently the growth cartilages cease to proliferate and become heavily calcified This line appears as a scar in the bone when growth is resumed Harris states

that such lines differ histologically only in extent from the lines of complete cessation of growth which result from final calcification of the epiphyseal junction Premature complete ossification of the growth cartilages, resulting in dwarfism, has been known to occur in children, who have suffered during the second decade from a series of severe infections, particularly the exanthemata

Heredity

It is a matter of common observation that heredity exerts an important effect on the growth of individuals This hereditarial influence has been associated by some authorities with the endocrine make up of the individual Although endocrine constitution is determined for the most part by heredity there are apparently other factors which affect the growth tendencies of the living organism A number of investigators among them Harrison [1], have demonstrated in their experimental work on the transplantation of limbs that these and other structures from two different sized species grow differently according to an individual capacity determined genetically in spite of an identical endocrine environment

The Endocrine Glands

The Adenohypophysis

The regulation of body growth and size is to a large extent, dependent upon the adenohypophysis This concept took form over a number of years as the result of clinical and pathological observations in giantism acromegaly and dwarfism in addition to physiological and biochemical studies of adenohypophysial function Among the outstanding contributions to this field have been the observations of Evans and Long and Stockard [2] The former demonstrated that daily long continued intraperitoneal injections of an adenohypophysial extract induced giantism in rats The growth curves of these experimental animals showed a steady continuance of growth as compared with the plateau of growth ordinarily encountered in untreated normal controls which reach adulthood These giant rats were proportioned symmetrically and weighed double that of their litter mates Roentgenological study of the giant skeletons disclosed that the normal size was exceeded by one and one half times Stockard s contributions, which were based on an extensive and fruitful experience are concerned with the constitutional and genetic aspects of the growth problem His concepts of the nature of growth are discussed in another connection in this chapter

Available evidence indicate that the adenohypophysis induces its effects by regulating growth largely through direct action on the tissues of the organism

but it also affects growth to some extent indirectly through the thyroid the gonads the pancreas and the adrenals which are under its physiological jurisdiction The fact that the function of the adenohypophysis is in turn subject to regulation by these and other glands of internal secretion complicates the problems of growth beyond our present ability to understand them completely

Experimental laboratory studies in this field apparently began in 1909 with Aschner s demonstration [4] that ablation of the dog s hypophysis results in dwarfism His observations were fully confirmed and extended subsequently by Smith [6 7] and Allen who worked with tadpoles and rats and by Crowe, Cushing and Homans[1] and Benedict and Thomas [1] who experimented with dogs Similar findings for other vertebrates including primates have appeared since then in the literature along with improvements in as well as new procedures for the technic of hypophysectomy[3 33 34 3]

The age of the animal at the time of hypophysectomy determines to some extent the effect of this operation on growth and body weight Hypophysectomy of immature rats 50 grams or less or of young rats before reaching their growth plateaux 80 to 120 grams results in the loss of only a small proportion of their original weight immature rats may even regain or exceed their preoperative weight level before growth stasis becomes complete Complete hypophysectomy in adult or almost full grown rats results in prompt cessation of skeletal growth which is due to failure of development of the cartilage cells in the epiphyseal discs[37] In addition there is a significant loss of body weight which is fairly rapid during the first few days after operation after which it becomes perceptibly slower until a level is reached some 20 to 40 per cent below the weight before operation[3 33 3 38 30] The loss in weight of the visceral organs is relatively greater than that of the other soft tissues These data obviously have an important bearing on the type of clinical disorders which may be expected from serious interference with or complete destruction of adenohypophysial function by pathological processes For instance complete ablation of adenohypophysial function in infancy or childhood ordinarily results in dwarfism uncomplicated by disorders of nutrition whereas similar pathology in the adult leads in certain circumstances to Simmonds cachexia

Disabilities resulting from hypophysectomy and their repair by appropriate replacement therapy have added further evidence to the many bonds linking the *adenohypophysis to body growth The administration of* adenohypophysial extracts containing the so called growth hormone *or the implantation of fresh* adenohypophysial substance induce a resumption of growth in the skeleton, the viscera and the other body tissues of hypophysectomized animals according to the observations of Smith[40] Reichert [1] Reichert Simpson Cornish and Evans[4] and Evans Pencharz Simpson and Meyer[43] In studies of this problem Thompson

that such lines differ histologically only in extent from the lines of complete cessation of growth which result from final calcification of the epiphyseal junction. Premature complete ossification of the growth cartilages, resulting in dwarfism, has been known to occur in children, who have suffered during the second decade from a series of severe infections particularly the exanthemata.

Heredity

It is a matter of common observation that heredity exerts an important effect on the growth of individuals. This hereditarial influence has been associated by some authorities with the endocrine make up of the individual. Although endocrine constitution is determined for the most part by heredity there are apparently other factors, which affect the growth tendencies of the living organism. A number of investigators among them Harrison [1] have demonstrated in their experimental work on the transplantation of limbs that these and other structures from two different sized species grow differently according to an individual capacity determined genetically in spite of an identical endocrine environment.

The Endocrine Glands

The Adenohypophysis

The regulation of body growth and size is to a large extent, dependent upon the adenohypophysis. This concept took form over a number of years as the result of clinical and pathological observations in giantism acromegaly and dwarfism in addition to physiological and biochemical studies of adenohypophysial function. Among the outstanding contributions to this field have been the observations of Evans and Long and Stockard. The former demonstrated that daily, long continued, intraperitoneal injections of an adenohypophysial extract induced giantism in rats. The growth curves of these experimental animals showed a steady continuance of growth as compared with the plateau of growth ordinarily encountered in untreated normal controls which reach adulthood. These giant rats were proportioned symmetrically and weighed double that of their litter mates. Roentgenological study of the giant skeletons disclosed that the normal size was exceeded by one and one half times. Stockard's contributions, which were based on an extensive and fruitful experience are concerned with the constitutional and genetic aspects of the growth problem. His concepts of the nature of growth are discussed in another connection in this chapter.

Available evidence indicate that the adenohypophysis induces its effects by regulating growth largely through direct action on the tissues of the organism,

that true growth always is associated with the acquisition of body protein, tha changes in protein metabolism may be regarded as an accurate index to an important aspect of the growth process and that the adenohypophysis influences growth by virtue of its effect on protein metabolism

The injection of adenohypophysial extracts rich in growth promoting activity is accompanied by striking changes in protein metabolism A single injection significantly reduces the blood non protein nitrogen urea and amino acids in dogs and fasted rats[8] [68] and causes a marked decrease in the excretion of urinary nitrogen in normal [1] and phloridzinized dogs [3] and in fasted rats[6] The decrease in the blood level of non protein nitrogen urea and amino acids occurs within a few hours of hormone administration and may persist for some time[69] Schaffer and Lee[7] [3] have found that such injections cause a small decrease in the amino acids and urea content of the carcass and a much greater fall particularly of urea in the liver Prolonged treatment keeps these liver constituents at consistently low levels Other investigations of the chemical composition of animals which have been stimulated to an increased growth rate by these extracts show that the proportions of water protein and mineral salts in the gained weight reverts to that of the extra uterine type characteristic of normal rapidly growing animals Consequently this gain in weight represents true growth The weight of evidence indicates that the growth hormone causes either an increased synthesis of protein or decreases the normal rate of protein catabolism Lee believes that the anabolic action of the growth hormone is first to conserve and increase the so called deposit reserve or storage protein and to decrease the exogenous catabolism of amino acids This stored protein probably is then incorporated into the less labile structural protein of the body by a process which may or may not be affected specifically by the growth hormone

The reverse of this metabolic picture is to be found in the hypophysectomized animal Perla and Sandberg[74] found an increased excretion of urinary nitrogen in hypophysectomized rats whereas young growing animals are always in positive nitrogen balance So far as fat metabolism is concerned changes in the body composition of operated rats indicate that there is relatively little demand on stored fat for energy purposes whereas protein reserves are primarily mobilized and consumed[8] The normal rat on a restricted diet which is comparable to that voluntarily taken by a hypophysectomized animal utilizes fat stores for energy body protein being spared[8] The injection of growth hormone converts this metabolic picture to that of the actively growing young animal The foregoing data on fat catabolism dovetail neatly with the observation that the energy requirements of the rat during the administration of a growth promoting adenohypophysial extract is satisfied largely by the fat stores and that body protein is stored[4]

ing from insulin administration is principally responsible for the gain in weight which is observed after insulin therapy Insulin, however, has other physiological effects, which contribute at least as much, or even more, to its clinical usefulness in malnutrition It promotes the utilization of available stores of glycogen for energy, aids in the storage of liver glycogen induces nitrogen retention and plays an important role in the conversion of carbohydrates to fat[64 6] It is probable that these effects play a more important role than the increase in appetite in so far as the clinical usefulness of insulin administration in malnutrition is concerned

The Gonads

The growth response to injections of an adenohypophysial extract is not modified appreciably by the absence of the gonads[4], although the state of function of the gonads significantly influences the rate of growth In the human precocious puberty is associated clinically with dwarfism due to premature ossification of the epiphyses whereas a form of giantism in which the epiphyses remain ununited, is induced by castration or the occurrence of eunuchoidism before maturity[66 67 68] A more detailed discussion of gonadal influence on growth is to be found in a subsequent part of this chapter

Summary — The available evidence thus indicates that the thyroid adrenal cortex pancreas and gonads can modify the growth process to a striking degree that the growth promoting or nitrogen retaining properties of the adenohypophysis are not mediated through these glands and that the secretions of these four glands are essential to the optimal growth promoting function of the adenohypophysis One may infer from the foregoing data and conclusions that these various hormones possibly in definite proportions to each other, occupy a crucial position in a complicated well integrated series of chemical reactions, which are concerned with the metabolism and more specifically, the growth of protoplasm

THE METABOLIC AND PHYSIOLOGICAL EFFECTS OF ADENOHYPOPHYSIAL EXTRACTS

On Protein and Fat Metabolism

Growth is a biological phenomenon characterized by a complex group of biochemical reactions which result in the synthesis of essential protoplasmic constituents and their incorporation into an integrated functional unit the cell Little is known of the mechanism by means of which these are accomplished, but certain aspects of it particularly in relation to adenohypophysial function, are coming rapidly to light It is clear from that which has been recounted already

tion against the expected thyroid atrophy Perla[81] subsequently confirmed the foregoing observations of splenomegaly in animals treated with adenohypophysial extract and observed also that hypophysectomy in rats is followed by a progressive atrophy of the spleen which is repaired by adequate replacement therapy

The fact that the liver of an animal treated with adenohypophysial extract enlarges out of proportion to the rest of the viscera or the body may be of special significance inasmuch as the liver is concerned with the most important aspects of protein metabolism Deamination of amino acids is dependent upon the presence of the liver which is also the most important if not the only site of urea formation in mammals Furthermore the blood protein fibrinogen is synthesized only in the liver [2]

The enlarged livers of those animals which were treated with such extracts retain the normal architecture of this organ and neither the hepatic cells nor their nuclei differ in size from those in normal control animals These findings taken in conjunction with the fact that the number of liver cells per gram of tissue remains unchanged [5] indicate that true hyperplasia has been induced by the adenohypophysial extract Since similar results have been obtained with purified thyrotropic hormone and thyroid hormone it is probable that the adenohypophysial growth factor is not primarily responsible for the hepatic hyperplasia[86]

On Skeletal and Integumentary Tissues

The skeletal deformities and skin changes which are among the salient findings in human giantism and acromegaly find their counterpart in the experimental syndrome induced by adenohypophysial extract The acromegalic bull dogs prepared by Putnam Benedict and Teel [2] exhibited the extraordinary soft tissue hypertrophy and marked thickening and local deformities of the long bones which are characteristic of human acromegaly In less constitutionally predisposed dogs such as shepherds Evans and his coworkers noted thickening and enlargement of the skull bones without appreciable change in the long bones The achondroplasic short extremities of the dachshund were unaffected by extract therapy

Mortimer's[87] studies of the skulls of hypophysectomized rats and of rats treated with adenohypophysial extracts are of special interest to the clinician in view of the skeletal abnormalities which characterize the disordered growth in acromegaly giantism and dwarfism Hypophysectomy results in skull changes which are more marked the earlier in life the gland is removed In very young animals the skull continues to increase in size slowly and in a modified manner since growth does not cease entirely because of the inherent capacity of young tissues to grow even in the absence of the adenohypophysis[87] The cranium grows

On Special Organs Other than the Endocrine Glands

Highly purified adenohypophysial extracts of the growth hormone were not available for experimental use until relatively recently Consequently most reported observations have been made with relatively crude extracts of this gland The interpretation of the results of these experiments is difficult in view of the characteristic secondary tropic effects which in turn induce widespread metabolic changes Nevertheless the results of such experiments closely parallel the pathological and clinical findings in giantism and acromegaly, possibly because the disordered adenohypophysial function in these diseases yields a secretion, which is comparable to that of the chemically crude extracts in experimental use The effects of these extracts in experimental animals have been particularly striking in the case of the visceral organs and skeletal system

On Visceral Organs

Putnam Benedict and Teel[51] observed a remarkable splanchnomegaly in a dog made acromegalic by treatment with such an extract The body weight of the animal at autopsy was 1 87 times that of its control litter mate sister The ratios of the weight of its visceral organs to those of the control were increased proportionately more with the exception of the spleen viz liver 3 42 lungs 3 36 pancreas 2 67 kidneys 2 43 heart 2 23 and spleen 1 16 There was also some increase in the connective tissues content of all the organs in the treated animal The adrenals contained cortical adenomas and the renal glomeruli and tubules were markedly hypertrophied The subcutaneous and omental fat deposits were notable for their paucity Downs [5] and Friedgood [6] also noted a disproportionate increase in the size of the liver in mice and guinea pigs respectively after treatment with adenohypophysial extract These investigators found a central necrosis in the livers of these animals Friedgood reported later [7, 8, 9] that marked enlargement of the adrenals due to cortical hypertrophy resulted from daily injections of an alkaline extract of the adenohypophysis This statistical study also disclosed that splenomegaly was an obvious but less consistent, feature of the experimental sydrome The splenomegaly was encountered far more frequently among the male than the female animals although the mean weight of the normal female spleen was found to be significantly greater than that of the normal male spleen There was no evidence that hypertrophy of these organs was related to the concurrent hyperthyroidism evoked by the extract This conclusion was substantiated by Collip Anderson and Thompson[80] who showed that the adrenocortical atrophy resulting from hypophysectomy can be obviated completely by daily injections of an adenohypophysial extract which is without similar protec

of endocrine dysfunction, in whom the histology of the adenohypophysis is fairly normal There are many breeds of dogs however, which are characterized by *peculiarities of type and distortions of form and growth which closely resemble* certain pathological conditions found in human families e g achondroplasia dystrophia fetalis, giantism and hypophysial dwarfism These structural abnormalities are associated with pronounced histopathological changes in the adenohypophysis which in ordinary circumstances might be held responsible for them

These various considerations led Stockard to make observations on the genetic developmental, anatomical and physiological characteristics of several highly modified dog breeds bred selectively over innumerable generations in order to perpetuate for dog fanciers reproducible types of localized skeletal deformities and generalized disorders of growth

A study of the development and adult condition of the bulldog s skull the bassethound s fore and hind limbs and the entire skeleton of the dwarf Pekingese dog disclosed that these skeletal structures are similar in each instance to those of the achondroplasic dwarf The adenohypophysis of the bulldog shows far reaching structural abnormalities whereas the bassethound s adenohypophysis adheres very closely to the normal canine pattern as represented by the German *shepherd dog None of these hypophyses were of a fixed pattern The histology* of the gland varied among the individuals of each dog breed but in spite of this individual variability the hypophyses from contrasted breeds presented histological patterns which were quite consistently different in detail Stockard also noted that the physical form and type of the individual could be correlated with the histological pattern and cellular nature of the adenohypophysis In a two and one half year old female bulldog Stockard demonstrated widespread cystic formations in the pars distalis an abnormally small amount of secretory epithelium in the pars tuberalis and pars distalis and an excessive amount of connective tissue separating the cord like arrangement of epithelial cells of the pars distalis The acidophiles stained brightly and occurred in unusually high proportions in relation to the basophiles By crossing such an English bulldog with the bassethound Stockard separated and sharply localized each of their achondroplasic characters in the succeeding generations and he demonstrated that achondroplasic dwarfing could occur in certain parts and acromegalic overgrowth in other parts of the *skeleton of the same individual He concluded from these experiments that the* growth response of certain parts of the skeleton to an altered adenohypophysial secretion depended primarily on the genetic constitution of the tissues Some individuals among the F hybrids of this cross resembled either one or the other of the parent stocks in physical form as well as in histological pattern of the adenohypophysis There were also some odd individuals among these F_2 hybrids

mediated by a variety of adenohypophysial hormones, which differ in their quantitative effects, depending upon the type of animal to which, and the circumstances in which, they are administered. He states[1 1 3] that the thyrotropic hormone and prolactin both play a part and act as mutual synergists in the growth of dwarfed mice whereas in pigeons prolactin alone is the growth promoting agent.

Constitutional and Genetic Concepts

Stockard[3] departs from this conventional dispute by refuting completely the concept of an adenohypophysial, growth promoting hormone. He states that growth is a universal property of protoplasm or life itself and occurs even where no specific adenohypophysial hormone is known to exist. He admits, however, that in higher animals the kind and degree of growth can be regulated and modified by such a secretion. Contrary to the generally accepted view Stockard believes that the adenohypophysis secretes a substance, which limits or inhibits rather than promotes growth and which regulates the amount of tissues and the size of organs by delicately balanced adjustments in the organism as a whole. In so far as this so called growth hormone contributes to the normal balance of the internal chemical environment it secondarily influences the growth of tissues, which already have been committed genetically to a characteristic growth response. Thus the transplantation of a Boston terrier hypophysis into a hypophysectomized dachshund could not possibly transform the dachshund into a Boston terrier. According to Stockard both the distortions of growth and the adenohypophysial pathology to which they are attributed ordinarily arise primarily from a constitution determined genetically. The experimental evidence marshalled in support of this hypothesis is impressive. Stockard's conception of the functional and genetic relations of the adenohypophysis was not completely recorded because of his untimely death. A review of his writings, however, gives a fairly precise notion of the thoughts he entertained on this subject. He emphasized that the tendency to produce races and individuals of widely different types and size is especially characteristic of the human species and the dog. Among human beings the most exaggerated deviations of type and constitution, e.g. giantism, dwarfism and acromegaly are associated with various pathological and functional changes in the endocrine glands. From a clinical viewpoint it has been customary to attribute such marked changes in physical type to the diseased gland. As a rule the emphasis has been placed on the functional deviations of the endocrines rather than on the hereditary element particularly in acromegaly. In certain instances however there is every indication that hybridization or other genetic modifications play an important role in the pathogenesis of these maladies.

There are some dog breeds which are free of skeletal deformities or symptoms

intimately correlated products of an hereditarial genetic background He believed that these three factors affect one another under the influence of an internal chemical environment the composition of which is regulated and controlled by the endocrine glands His observations indicate furthermore that the structural pattern and functional activities of the endocrine glands also are inherited characteristics and that a highly significant correlation exists between the inheritance of skeletal deformities and the occurrence of defective development of the adenohypophysis It may be inferred from Stockard s studies that any genetic change *or mutation, which affects the endocrines either directly or indirectly probably is of the utmost importance in giving rise to a new species as well as to a new* domestic breed His correlation of hybrid types and adenohypophysial histology clearly links body type and hypophysial pattern very closely

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who differed considerably from the parent stocks and developed growth deformities foreign to both breeds These unusual distortions of growth, commonly encountered in other breeds apparently arose from new combinations of qualities F hybrids of the achondroplasic bulldog bassethound stocks sometimes exhibited evidence of acromegaly in the form of excessive overgrowth and wrinkling of the skin heavy large bones of coarse structure, enlarged skull and malocclusion of the teeth F_2 hybrids also showed frequent abnormalities of their endocrine glands which included cryptorchid testes and cystic or arrested and otherwise modified development of the adenohypophysis In the adenohypophysis of one of these F hybrids which resembled an acromegalic St Bernard, Stockard found an almost perfect replica of the histological picture characteristic of human acromegalic giantism i e acidophilic adenoma or true hyperplasia of the acidophiles There were very few chromophobes in this species, and basophiles were hard to find Thus an acromegalic constitution was brought about through complex combinations of qualities in the bassethound bulldog F hybrids, which are derived from essentially normal sized achondroplasic parent stock This cross also produces examples of dwarfism Stockard points out that these opposite types of growth response are associated with similar histological derangements of the adenohypophysis He denies therefore that adenohypophysial hypersecretion induces giantism and acromegaly and that its hyposecretion results in dwarfism This deduction appears to be the only obvious flaw in his argument against the existence of a growth stimulating hormone inasmuch as he assumes that gross histological similarities of the adenohypophyses necessarily indicate an identity of functional behavior Actually there is no cytological or physiological evidence among his observations to substantiate this viewpoint

Other experiments bearing particularly on the nature of giantism were carried out by Stockard on great dane and St Bernard dogs These animals are much larger in size than any of their probable ancestors The great dane is a slender gracefully proportioned giant whereas the skin and skeleton of the St Bernard who is a giant of heavy proportions exhibit definite evidence of acromegaly The adenohypophysis of the St Bernard is cystic very often or shows other signs of modified or arrested development The F hybrid generation resulting from a cross between great *dane and* St Bernard, shows a variety of combinations of the characters derived from the two pure stocks Among the various types which appear in the F generation are slender great dane like giants, giants with marked stigmata of acromegaly and adipose eunuchoid creatures which resemble Frohlich s syndrome in man

Having studied these interrelations of genetic constitution and endocrine activity on both normal and highly modified dog breeds Stockard concluded that the skeletal structure, physiological function and behavior of an organism are

intimately correlated products of an hereditarial genetic background He believed that these three factors affect one another under the influence of an internal chemical environment the composition of which is regulated and controlled by the endocrine glands His observations indicate furthermore that the structural pattern and functional activities of the endocrine glands also are inherited characteristics and that a highly significant correlation exists between the inheritance of skeletal deformities and the occurrence of defective development of the adenohypophysis It may be inferred from Stockard s studies that any genetic change or mutation which affects the endocrines either directly or indirectly probably is of the utmost importance in giving ri e to a new pecies as well as to a new domestic breed His correlation of hybrid types and adenohypophysial histology clearly links body type and hypophysial pattern very closely

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Part IV

CLINICAL DISORDERS OF GROWTH

Clinical Application of Physiological Principles

As one might anticipate from the delicately balanced highly integrated and complex activities of the adenohypophysis clinical evidence of disturbances in its normal functions are encountered not infrequently Prominent among these in interest if not in numbers are the disorders of growth Abnormalities of growth frequently are modified by conditions which are inherent in the functional pattern of adenohypophysial activity The clinical picture of the resultant syndrome thus is highly variable and depends to a considerable extent upon a number of factors of which the following are known well enough to record with some assurance

Disturbance of Growth regulation in Relation to Disorders of Carbohydrate, Water and Sex Metabolism

In addition to its growth regulating activities the adenohypophysial function frequently is upset coincidentally in other directions so that various combinations of disordered carbohydrate water and sex metabolism may become features of the clinical syndrome

Disturbance of Growth regulation in Relation to Functional Condition of Epiphyses

The physiological age of the individual as indicated by the state of epiphyseal diaphyseal union determines to a large extent the type of growth disturbance which can develop If the epiphyses are open and the growth regulating influence of the adenohypophysis is deranged in the direction of hyperfunction the clinical picture is that of giantism whereas if the epiphyses and diaphyses are united and the same hypophysial conditions prevail acromegaly is the end result When adenohypophysial hyperfunction begins before puberty and continues into adulthood the patient develops features of acromegaly in addition to giantism

Disturbance of Growth regulation in Hypogonadism

Primary hypogonadism, which is established before puberty, results in delayed union of the epiphyses and a clinical syndrome of eunuchism or eunuchoidism. By virtue of a secondary derangement of adenohypophysial function this combination of circumstances is favorable to the prolonged and consequently excessive stimulation of the growth cartilages of the long bones. The clinical picture of the resultant endocrinopathy is that of *eunucnoidal giantism*.

The abnormal persistence of unossified epiphyseal cartilages in castrated or eunuchoid individuals has been attributed universally to the absence or marked impairment of gonadal function. In support of this assumption it has been pointed out that precocious puberty is associated clinically with premature closure of the epiphyses and dwarfism, whereas normal sexual maturity likewise is related chronologically to epiphyseal union and cessation of growth. It is noteworthy, however, that the epiphyses of *infantilistic dwarfs* remain wide open far into middle age even though their growth may remain stationary. The only physiological denominator common to infantilistic dwarfism and eunuchoidal or castrate giantism is gonadal insufficiency. The only anatomical denominator common to both conditions is the persistence of ununited epiphyses. The outstanding difference between these two endocrinopathies obviously is the excessive linear growth in castrated or eunuchoid individuals and the stunted growth in victims of infantilistic dwarfism. Generally it is stated that excessive growth occurs in the castrated or eunuchoid individual because the epiphyses remain ununited. That this is an unacceptable explanation may be gathered from the fact that ununited epiphyses likewise are characteristic of infantilistic dwarfism. One may assume safely from available evidence that the presence or absence of a growth stimulus in an individual with ununited epiphyses determines whether the end result is dwarfism or a form of giantism. In the present state of our knowledge one may conclude that the same pathological process which deprives the dwarf of his growth stimulus also robs him of his gonadotropic hormones. The result is infantilism and dwarfism. In the castrated or eunuchoid individual, however, the pathology primarily is in the gonads which when removed or functionally incapacitated stimulate an intact adenohypophysis to increased activity. In this functional hyperactivity lies the probable explanation for the excessive linear growth in eunuchoidal giantism. It is generally accepted that castration results in basophilia of the adenohypophysis as well as in an increase of its gonadotropic potency[1, 3, 4, 5, 6, 7, 8]. The functional pattern of the hypophysis appears to be such that hypersecretion of one of its hormones not infrequently is associated with or responsible for an increase in the rate of secretion of another of its hormones. Although the growth hormone has been linked in many ways with the

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acidophile it should be recalled that the disturbances in secretion of the thyro tropic and sex hormones are reflected cytologically by alterations in both the acidophiles and basophiles While there is no evidence to suggest that the basophiles, which are hyperactive in hypogonadism, may play a role also in the regulation of epiphyseal growth neither is there any direct evidence against this thought A disturbance in the function of the acidophiles coincident with or secondary to that of the basophiles would of course explain the excessive growth stimulus in a more orthodox fashion The fact that gonadectomy affects the adenohypophysial acidophiles as well as the basophiles is in accord with the latter suggestion

Relation of Sex Hormones to Regulation of Growth

There have been isolated from the adrenal cortex certain chemical principles which exhibit the biological activity of hormones secreted by the male and female gonads These corticosteroids include the androgenic substances adrenosterone and 17 hydroxyprogesterone[9,10] and the ovarian like hormones estrone and pro gesterone[11,12] which show estrogenic and progestational activities respectively A gonadotropin adrenoluterin also has been isolated from the adrenal cortex[13] It is important to note furthermore that these steroids of the gonads and adrenal cortex are related chemically by virtue of their common molecular configuration, the phenanthrene cyclopentane or cholane nucleus The fact that varying amounts of biologically active androgenic and estrogenic steroids continue to be excreted in the urine after gonadectomy lends credence to the belief that the adrenal cortex may be regarded as a definitive organ of sexuality

As noted above precocious puberty is associated with premature closure of the epiphyses whereas normal sexual maturity likewise is related choronologically to epiphyseal union Growth ceases in both cases These clinical data, coupled with the fact that the epiphyses remain wide open indefinitely in castrated or eu nuchoid individuals who have little or no gonadal function have led to the widely accepted belief that sex hormones inhibit growth or at least are antagonistic to its progress There are other clinical observations however which not only fail to harmonize with this viewpoint but actually indicate that the sex hormones stimulate the rate of growth Rowlands and Nicholson[14] have reported an in creased rate of growth in boys afflicted with testicular tumors, which produced excessive amounts of androgen Tumors of the adrenal cortex likewise are as sociated with enhancement of the rate of linear growth but early closure of the epiphyses is another feature of this condition Friedgood and Gargill[15] observed these phenomena in a 10 year old female, who developed extensive evidence of virilism 6 months after she began menstruating precociously at the age of 8 as a result of an adrenocortical tumor These clinical data indicate that androgenic

substances of testicular origin stimulate the rate of linear growth of the body They suggest also that the adrenocortical steroids which exhibit androgenic and estrogenic biological properties are associated in some way with enhancement of the rate of growth and premature closure of epiphyse That androgens stimulate the rate of linear growth has been proved beyond doubt by the effect of testo terone compounds in dwarfed children The administration of testosterone propionate or methyl testosterone in such circumstances results in an obvious acceleration in the rate of growth [61, 28, 4, 9] There is no evidence that these hormones induce premature closure of the epiphyses[1] nor has this undesirable effect been elicited by injections of chorionic gonadotropin which stimulates the development of the testes and accelerates the rate of linear growth coincidentally [21] It is well recog nized of course that the onset of puberty which is characterized by evidence of enhanced androgenic and estrogenic activity in both sexes generally is the period during which there is an exaggerated spurt in the rate of linear growth In the light of present knowledge this may be attributed in part to a state of increased gonadal activity Experience with the skeletal changes in cases of adrenocortical tumor of which the case cited above is an example[15] suggests that the adenocorti cal androgens and estrogens, either in combination or individually also are con cerned with the normal physiological mechanism which regulates and controls the growth and maturation of epiphyses in adolescence In any event it is of impor tance in this connection to note that the adrenal cortex has been credited with the property of retarding the rate of epiphyseal chondrogenesis and osteogenesis in hibitory effects which stunt the body growth [3]

The Problem of Prepubertal Gonadal Function in Relation to Growth

There is one aspect of the relation between gonadal function and growth which needs further elucidation It is assumed generally either overtly or tacitly that the gonads are lacking in function until puberty arrives and objective evi dence of their functional activity is to be seen in the blossoming of secondary sexual characteristics Such a viewpoint was expressed by Severinghaus in the statement Since the ovaries do not begin active follicular growth until about the twentieth day the young female rat may be regarded as a physiological cas trate It is possible however that the gonads may be functioning at a reduced level of activity prior to puberty The three so called springing up periods to which reference has been made already suggest that a growth promoting stimu lus goes into high gear on two occasions long before puberty is due Whether or not these are an expression of a temporarily heightened gonadal influence remains to be seen At any rate the subject is still too unexplored to merit a dogmatic attitude

ACROMEGALY

Definition

Acromegaly is a chronic disorder in which the adenohypophysis always is involved pathologically This syndrome ordinarily is attributed to a benign or malignant acidophilic adenoma only infrequently is it associated with simple hyperplasia of the acidophilic cells of the adenohypophysis Experimental genetic studies indicate that the adenohypophysial pathology as well as the constitution of the afflicted individual may be inherited characteristics The disease is characterized by hypertrophy of the skeleton, overdevelopment of the soft parts, splanchnomegaly and pathological as well as physiological changes in many of the glands of internal secretion other than the adenohypophysis, especially the thyroid adrenal cortex, parathyroids thymus and gonads

Historical Background

Acromegalics as well as giants have been objects of interest to the layman and artist since prehistoric times According to Sternberg [5, 6] a portrait of an acromegalic painted in 1553 is the earliest known record of this disease The pathology of acromegaly was described clearly by Fritsche and Klebs several years before Marie [8] in 1886 recognized and named the clinical syndrome The following year Minkowski [9] ascribed the syndrome to hypophysial disease In his original communication Marie reported 2 cases of his own and collected 5 others which had appeared previously in the literature under various names, and in subsequent publications[10, 11] which increased the number of his reported cases to 17 he also directed attention to the enlarged hypophysis as a pathogenetic factor in the disease Marie s contributions stimulated the appearance of increasing numbers of reported cases

By 1893 Collins had 83 cases available for review, and in 1897 Sternberg [5, 6] collected 200 cases of which 47 had been autopsied In 1932 Atkinson [4] analyzed the data on 1 319 cases with 265 autopsies Benda[35, 36] was the first to direct attention to the predominance of acidophilic cells in the adenohypophysial adenomas in 3 of the 4 cases he reported In spite of Benda s report and Fischer s[37] subsequent emphasis of this point there was considerable controversy over the pathogenesis of this disease until those earlier pathological studies were reviewed and extended by the investigations of Cushing Bailey Davidoff and Putnam[38, 39, 40], who were in better position to interpret the physiological and clinical significance of their observations

Incidence and Predisposing Factors

Acromegaly is a rare disease. Atkinson[4] uncovered only 1 606 instances of this disease after a careful search of the literature up to 1938 in addition to the aid of the British Consular Service all over the world. Autopsies had been performed on less than 25 per cent of these cases. At the University of California Hospital over a 5 year period from 1937 to 1941 12 cases were so diagnosed among 35 757 entries or an incidence of 1 in 3 000. The diagnosis was made only 14 times among 210 094 admissions to the Boston City Hospital over a 6 year period from 1930 through 1935.

Males and females are about equally affected and it may occur in the black and yellow races as well as the white. Cases have been reported in late childhood but they are certainly exceedingly rare before the second decade. The onset occurs in the third decade in about 50 per cent of the patients.

The only predisposing factor known is that of familial tendency. A history of acromegaly or of various types of hypophysial disease in other members of the family is obtained sometimes[3, 3, 36, 11, 4, 3, 45]. Benda[5, 6] reported 4 cases in one family.

The onset of the disease may be preceded by or coincide with trauma to the skull, pregnancy or an acute infectious disease, but there does not appear to be any detectable precipitating factor in the majority of cases.

Correlation of the Pathology and Pathological Physiology. Their Clinical Significance

The Adenohypophysis. — The hypophysis rarely is of normal size in acromegaly. Ordinarily it is enlarged because of a benign adenoma or malignant neoplasm. These tumors, which usually are solid, not infrequently are softened by cystic or hemorrhagic areas. Generally the tumors are relatively small, in which case they may extend above the diaphragma sellae or less frequently into the sphenoid cells. Rarely they become enormous, erode the sella turcica and invade the cranial cavity. The common cytological denominator of the normal sized as well as the tumorous hypophysis is hyperplasia of the acidophilic cells[39, 46, 47, 48]. According to Putnam and Davidoff the tumors are of three different types. Type I consists of a highly cellular, loose mass of large cells, practically all of which are packed with acidophile granules. Most of the cells have hyaline centers, many are multinucleated. The tumors of type II, although practically free of stroma like those of type I, differ from the latter in that the mass is more compact and many non granular cells occur among those which are acidophilic. In tumors of type III there is only a thin rim of cells containing acidophile granules

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Date	B M R	Pulse Rate	Therapy	Experimental period in days	Comment
5/2/30	+43	95	None		Control
7/30/30	+39	92	None		Control
7/30/30	—	—	Lugol s solution 10 drops twice daily	0	Lugol s solution started immediately after last B M R determination
8/5/30	+38	92	Increase Lugol s solution to 15 drops, twice daily	6	
8/6/30	+32	80		7	
8/7/30	+25	76		8	
8/9/30	+24	80		10	
8/12/30	+27	80		13	

Iodin induced a progressive decrease in basal metabolic rate to a level of +18 per cent in 9 days after which the rate of oxygen consumption returned to a level of approximately +30 per cent in spite of continued iodin therapy Davis[5 54] has reported 3 cases of acromegaly treated in similar fashion and observed only a moderate decrease in the rate of oxygen consumption in one of them The significance of adenohypophysial hyperactivity in relation to the hyperthyroidism of acromegaly is demonstrated further by the observations of Cushing and Davidoff[5 6], who found that operations on the chromophilic hypophysial adenoma itself was followed by a decrease in basal metabolic rate which was almost as uniform as the effect on metabolism of thyroidectomy in exophthalmic goiter Their data indicate however that the elevated oxygen consumption in acromegaly usually is not reduced to normal by thyroidectomy This is in accord with what is known of the extrathyroidal metabolic effects of the adenohypophysis[57 58 59]

In attempting to evaluate the incidence of goiter and hypermetabolism in acromegaly it is essential to recall that the onset of this disease is insidious that the course is one of prolonged duration and that it is marked by unpredictable waves of remissions or exacerbations Since studies of individuals with this disease ordinarily are made at times when pressure symptoms in or about the sella turcica physical disfigurement or cardiac complications call the patient s attention to his ill health it is possible that episodic disturbances in thyroid physiology may be overlooked Furthermore, many patients are relatively well advanced in their course before they come under observation and it is well known that the hyperthyroidism in such circumstances is quite likely to have disappeared or to have been replaced by hypothyroidism The foregoing considerations may well

around a central mass of small agranular cells The clinical activity of the disease is said to be proportional to the number of acidophilic cells found in the adenohypophysis[40]

Pathological changes are to be found in endocrine organs other than the adenohypophysis These alterations appear for the most part to be secondary to the hypophysial pathology

The Thyroid —In 1897 Magnus Levy ' pointed out that certain physical signs and symptoms characteristic of exophthalmic goiter also are to be found associated inconstantly with acromegaly Enlargement of the thyroid gland, elevation of the basal metabolic rate and tachycardia not infrequently complicate the clinical picture of acromegaly during the active phases of this disease, exophthalmos is an unusual but occasional physical finding The basal metabolic rate varies tremendously so that reports of arithmetic means on large groups of patients are misleading and have no significance other than to indicate that there is a definite trend towards hyperthyroidism in the early phases of acromegaly and towards hypothyroidism in the late stages The range covered is from —30 per cent to +80 per cent and the rate in any one individual apparently depends on the duration of the disease and the state of adenohypophysial function As the activity of the chromophilic adenoma burns itself out and the remainder of the hypophysial parenchyma is destroyed by pressure atrophy, the acromegalic develops a secondary hypothyroidism Discovery of the thyroid stimulating effect of adenohypophysial extracts and the fact that thyroid atrophy results from hypophysectomy have established a rational explanation for the occurrence of hyperthyroidism in acromegaly Probably it is due to stimulation of the thyroid gland by an excessive secretion of the adenohypophysial thyrotropic principle, and the ophthalmotropic activity of the adenohypophysis[51] could account satisfactorily for the exophthalmos which is encountered occasionally This parallelism between the hyperthyroidism of acromegaly and that of exophthalmic goiter is enhanced further by the observation that iodin induces an identical decrease in the elevated basal metabolic rate of both diseases In 1927 Cushing and Davidoff reported a case of acromegaly in which iodin decreased the elevated basal metabolic rate just as it does in exophthalmic goiter and in 1930 Friedgood [2] encountered a second early instance of acromegaly before erosion of the dorsum sellae was detected which responded in a similar fashion The diagnosis was confirmed subsequently at autopsy An abbreviated tabular protocol of this case follows

A third case of acromegaly with hyperthyroidism which responded favorably to iodin therapy came to this writer s attention through the courtesy of Dr James H Means The initial basal metabolic rates ranged from +30 to +45 per cent with an average of +39 per cent on four successive determinations

dial failure than the hyperthyroidism It is probable however that hyperthyroidism also is an important contributing factor Adequate treatment of the myocardial insufficiency depends therefore on the control of the hyperthyroid state as well as of the hyperactive adenohypophysial condition

The Parathyroids —Enlargement of the parathyroids in acromegaly was described originally by Erdheim[69] and adenomas of this gland have been reported occasionally according to Cushing and Davidoff [6] Hadfield and Rogers [0] on the other hand, have questioned the pathological diagnosis of adenoma That this parathyroid pathology may be related to perverted adenohypophysial function is suggested by observations on experimental adenohypophysial hyperactivity Adenomas of the parathyroids have been found in experimental acromegalic animals [9], and adenohypophysial extracts similar to those which have produced the latter also induce hyperplasia of the parathyroid in rabbits [1] Friedgood and MacLean [5] [4] have demonstrated an elevated blood calcium level in guinea pigs subjected to treatment with alkaline extracts of the adenohypophysis The blood phosphorus level was not altered coincidentally

The Adrenals —The adrenals particularly the cortex ordinarily are enlarged markedly in acromegaly Microscopic and macroscopic cortical adenomas are frequent findings Here as in the case of the thyroid and probably of the parathyroids it is likely that an overabundant adenohypophysial secretion is at fault In 1929 Putnam Benedict and Teel observed adrenocortical adenomas in dogs which were injected over a period of months with an alkaline extract of adenohypophysis In 1932 Evans and associates [5] noted that the injection of growth promoting extracts resulted in cellular hypertrophy of the fasciculate zone of the adrenal cortex with some increase in the amount of cortical lipoids In 1933 Emery and Atwell[77] Friedgood[74] [8] and Houssay and associates [9] reported independently that the daily injection of only partially purified adenohypophysial extracts caused a marked hypertrophy and hyperplasia of the adrenal cortex which was significant statistically[74] This was confirmed abundantly by numerous subsequent investigators with more highly purified adenohypophysial extracts containing the adrenocorticotropic hormone A detailed account of the latter is included in a discussion of the adrenocorticotropic hormone in Part II

The Gonads —The ovaries and testes have been regarded generally as atrophic although there are no adequate clinical or autopsy records to substantiate this viewpoint As a matter of fact hypergenitalism in the male acromegalic with hypertrophy of the testes is not an infrequent clinical observation In one of the cases reported by Cushing and Davidoff [6] there was an hypertrophy and in another an atrophy of the spermatogenic epithelium and interstitial tissue Teel has observed hypertrophic changes in the female generative tract Schultze and Fischer state that in a man of 56 in whom the acromegaly was of seven years

account for whatever discrepancies there are in the literature on the incidence of clinical hyperthyroidism in acromegaly Davidoff found thyroid enlargement present in 25 per cent of 100 cases Davis in 50 per cent of 166 cases[4, 55] and Cushing and Davidoff[8] reported an elevated basal metabolic rate in 70 per cent of 72 patients Boothby and Sandiford[61] observed hyperthyroidism in 50 per cent of 30 cases

Enlargement of the thyroid may be diffuse early in the disease, but simple hypertrophy and hyperplasia are encountered uncommonly, probably because thyroidectomy usually is not done until relatively late in the disease The histological appearance of the enlarged thyroids varies considerably The most common finding is that of fairly well circumscribed nodules of parenchymatous hypertrophy and hyperplasia scattered throughout the substance of a colloid gland or a gland which is itself the seat of widespread hypertrophic and hyperplastic parenchymatous changes Colloid degeneration is met with frequently and is the end result of a succession of many periodic waves of activity alternating with involution This cyclic variation in thyroid function apparently is a reflection of the successive remissions and exacerbations characteristic of the course of acromegaly In accordance with the observations of Marine and Lenhart[8, 63, 64] and Reinhoff[65, 66, 67] these alternating phases of thyroid activity, hypertrophy and hyperplasia followed by the colloid state etc probably result in the so called adenomatous goiter Certainly such nodular areas do not represent true tumors such as the adenomas They are localized regions of hypertrophy and hyperplasia set off from the surrounding parenchyma by connective tissue This type of goiter is the most frequent form of thyroid enlargement in acromegaly Those instances in which the thyroid gland is of normal size can be explained satisfactorily by a fundamental rule of hypophysial physiology viz when one of the several functions of the hypophysis is disordered the gland may or may not exhibit a concomitant disturbance in the secretion of one or more of its other physiologically active substances The pattern of dysfunction i e the number and type of physiological disturbances is unpredictable in any one case and varies from patient to patient It is also possible that pressure atrophy may interfere with the excessive elaboration of the thyrotropic hormone early in the course of the disease thus obviating the abnormal stimulation of the thyroid gland

Since myocardial insufficiency not infrequently is a complication of persistent hyperthyroidism it might be anticipated that its incidence would be relatively high in acromegaly Courville and Mason[68] have found that among 24 cases of this disease 6 died of cardiac failure and 18 showed some evidence of it during their period of observation They concluded however that the increased work imposed on the heart by the generalized splanchnomegaly and overgrowth of the heart itself were quite likely the more immediate factors responsible for myocar

largement of the external occipital protuberance increases the circumference of the skull significantly and alters the physiognomy of the patient to a remarkable degree The disproportionate enlargement of the mandible results in marked malocclusion The teeth become widely separated not so much due to the en largement of the jaws as to a heaping up of the alveolar arches[5]

The bones of the extremities generally are enlarged in diameter because of overexpansion of the cancellous bone in addition to an increase in periosteal bone growth The latter appears to be due to an abnormal exaggeration of the normal transverse growth of bone whereas in giantism there is an increased cartilaginous bone growth which results from an abnormal exaggeration of normal longitudinal bone growth An increase in the length of the long bones also occurs in acromeg aly if the disease gets started before closure of the epiphyses Other evidence of abnormal proliferation of bone tissue occurs in the form of numerous wart like projections exostoses at the site of muscular and ligamentous attachments and around joints The surface of the bones is markedly irregular and rough at the ends of bones and wherever spongy tissue is abundant as in the vertebrae the basilar portion of the occiput and the bones of the feet Thickening of the bones is particularly apt to occur at the site of the fused epiphyses This terminal thick ening results in that tufting of the phalanges of the hands and feet which is roent genologically pathognomonic of the disease Erdheim[86] has described a form of arthritis in acromegaly which is caused by periosteal ossification with pathological proliferation of the cartilage

The vascular channels of the bones are visible and large The medullary canals of the diaphyses are dilated and so are the Haversian canals which appear on the surface in distinctly punctate form Fritsche and Klebs[7] have called special attention to the markedly dilated blood vessels in acromegaly

Roentgen Studies of Skeletal Abnormalities —Oppenheim[7] was the first to recognize enlargement of the sella turcica during life by means of roentgenography Since that time it has proved invaluable in the differential diagnosis of hypophysial disease[88 89 90 91 92 93 94] The x ray changes of the bone in and about the sella de pend for the most part on the direction in which the expanding tumor exerts its pressure Thus a purely sellar tumor may widen the sella and deepen the floor so that the bony partition between the sella and the sphenoidal sinuses is reduced to extreme thinness or to actual perforation The clinoid processes remain intact in such cases although the tumor is large Tumors which grow upward widen the entrance to the sella erode the clinoid processes and finally destroy them In a third variety there is more or less complete absorption of the dorsum sellae and a downward displacement of the base of the sella so that there is obliteration of the sellar landmarks with the usual exception of the anterior clinoid processes In some instances there is a downward displacement of the entire sphenoidal re

duration, there was strikingly abundant spermatogenesis and an enlarged prostate, which was in a condition of abundant secretion Atrophy of the internal genitalia has been reported in 36 4 per cent of the 118 female acromegalic patients according to Creutzfeld[81] Tandler and Grosz[5] found total regression of the primordial follicles and cessation of formation of the Graafian follicles They noted also degeneration of the interstitial cells of the testes and of the epithelium of the seminal vesicles Hypergonadism apparently is more common in the male than in the female, in whom there is a high incidence of amenorrhoea and other menstrual disorders It is not surprising that both hypertrophy and atrophy of the gonads occur in association with acromegaly they should not be regarded as mutually contradictory findings It is conceivable that in one phase of the disease the acidophilic hypophysial adenoma may be in a state of hypersecretion or cause an irritative hypersecretion of the surrounding glandular parenchyma, whereas later there is hyposecretion due to internal disintegration of the adenoma or pressure atrophy of the surrounding parenchyma, as the case may be

The Liver Spleen Kidneys Thymus and Pancreas — The thymus frequently is persistent and may be relatively much enlarged Generalized lymphoid hyperplasia often is an associated feature The spleen and kidneys may or may not be hypertrophied, but the liver usually is increased in size and in one instance[34] was found to weigh 6 200 grams in comparison with a normal weight of about 1 500 grams Cushing states[82] that with the exception of an unusual infiltration of fat no definite change was observed in the pancreas of 8 hyperpituitary individuals He adds that possibly in all of them the islets were more in evidence than in the average supposedly normal gland Goldberg and Lisser[84] report that in one diabetic acromegalic patient autopsy disclosed a few small islets in a gland which otherwise looked grossly normal

The Skeleton — The skeletal pathology of acromegaly has been studied most extensively by Sternberg [5, 26] The skeletal hypertrophy which is generally symmetrical is particularly well marked in the skull and extremities In advanced cases the entire skeletal system may be enlarged particularly in the transverse diameters and most of the cartilage of the body is ossified[40] The experimental form of acromegaly, which has been produced in animals by long continued injections of chemically crude extracts of the adenohypophysis is characterized by remarkably similar skeletal alterations These have been described in detail in a previous section of this chapter

The skull is affected in several ways The flat bones of the calvarium are increased in thickness and overexpansion of the cancellous bone is particularly notable in the prognathous mandible Hyperpneumatization of the skull occurs through enormous enlargement of the nasal sinuses and mastoid cells The gradual but progressive development of these changes in addition to a marked en

muscular stresses and strains induce scoliosis of the spinal column and deformity of the mandible other than its general enlargement

Skin Mucous Membranes and Connective Tissue — In addition to the general skeletal enlargement there is also a considerable thickening of the inter osseous connective tissue and of the overlying soft parts The skin may be raised readily from the underlying tissues in thick folds These external thickenings are

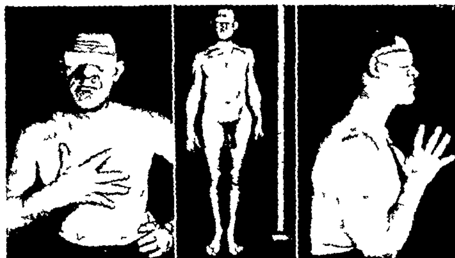


Fig 6 Acromegaly Note the hyperpigmented skin hypertrichosis coarse features of the physiognomy paw like hand the shape of the skull and mandible and the development of the genitalia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

largely responsible for the coarse features of the acromegalic and contribute to the configuration of the paw like hands and sausage shaped fingers (Fig 26) There is also an augmentation in the connective tissue of the subcutis which extends to and may involve the muscles The tissues thus feel dense and boggy to palpation and the natural lines and creases of the face and hands are increased to the depth of furrows particularly over the forehead

The size of the hair follicles is increased the papillae are hypertrophied and the sebaceous glands are enlarged and hyperactive The skin pigmentation becomes progressively deeper in the active stages of acromegaly in contrast to the ghostly pallor unrelated to anemia and probably due to depigmentation which is characteristic of adenohypophysial insufficiency Late in the disease, when glandular insufficiency supervenes, the acromegalic also acquires this abnormal skin pallor which may be accentuated by a secondary anemia

gion In the early stages of acromegaly particularly in the absence of a significantly enlarged hypophysial mass there may be thickening of the walls of the sella, probably as an expression of the general tendency toward osseous overgrowth In one instance case xxx cited by Cushing[54], there had been such a degree of bony overgrowth that the actual enlargement of the sella was masked until it was disclosed by stereoscopic plates Roentgenography is particularly helpful in the diagnosis if the tumor is calcified

Normal configuration of the sella turcica by x ray is not incompatible with the diagnosis of acromegaly, since this syndrome may be initiated without tumor formation by microscopic alterations in the adenohypophysis Furthermore an extrasellar acidophilic tumor arising in the sphenoidal sinuses from vestigial remnants of the so-called craniopharyngeal duct is believed to result in acromegaly Erdheim[69 86 89] reports such an instance in which the tumor eroded the floor of the sella from below and established contact with the hypophysis in this unorthodox fashion

The general configuration of the skull and the size of the sinuses yield important radiological information concerning one aspect of the adenohypophysial dysfunction in acromegaly[95 96] The skull shows widespread hyperpneumatization The frontal sinuses bulge and the mastoid cells and sinuses of the facial cranium are overdeveloped also These changes in addition to the overexpansion of cancellous bone in the lower jaw alter the radiological configuration of the face strikingly A diffuse generalized skeletal sclerosis which includes the skull, complicates these primary changes so that there is massive thickening of the cranium and other parts of the skeleton Although it has a special predilection for the mandible the overexpansion of cancellous bone is also of generalized distribution where it is characterized by marked bone proliferation in the region of the fused epiphyses and terminal phalanges Consequently there is marked thickening of the bones especially near the fused epiphyseal lines The overexpansion of cancellous bones in the hands and feet which takes place during the early stages of the disease subsequently is obliterated by the superimposed sclerosis and results in tufting of the phalanges which is a pathognomonic x ray sign

Osteophytes indistinguishable from those encountered in hypertrophic arthritis may extend into tendons and ligaments Occasionally they are extensive enough to fuse several vertebrae together These observations suggest that the adenohypophysis may be responsible for the hypertrophic arthritis of middle age inasmuch as the function of this gland is disturbed to a significant degree by the advent of the menopausal or climacteric period Other important changes occur in the spine which Atkinson[94] found affected in 80 per cent of the cases The vertebrae become enlarged in all diameters The most frequent deformity of the spine is an upper dorsal kyphosis with a compensatory lumbar lordosis Abnormal

Hair —The growth of hair on the head often is remarkably thick and the individual hair strands are coarse In males there is an increase in the hair of the trunk, abdomen and extremities where hair is already present or an ab normally heavy growth appears in these regions during the course of the malady The pubic and axillary hair growth characteristically becomes more dense In females there may be hair growth of a virilistic type and distribution in associa tion with an appreciable increase in the size of the labia majora and clitoris

Muscles —In most cases the muscle strength is not diminished in the initial stages acromegalic individuals sometimes may even exhibit extraordinary strength in the early stages of the disease Early in the syndrome, however there may be a gradually increasing fatiguability and eventually muscular weakness is a predominant debilitating symptom The muscles of the arms and legs be come markedly atrophic in the terminal stages a change which renders more con spicuous and serves to accentuate the bizarre skeletal deformities of this disease (Fig 27) Microscopically such muscles show an increase in their connective tis sue and fat content with degeneration and atrophy of the individual fibers [a]

Clinical Course

So diversified are the clinical manifestations of acromegaly that the pattern of the developing syndrome exhibits innumerable variations The complex symp tomatology can be accounted for on a rational physiological basis only by taking into consideration the following factors

(1) An expanding adenohypophysial tumor produces so called neighborhood signs and symptoms by virtue of the strategic anatomical position of the gland with reference to the surrounding osseous and intracranial structures

( ) The fact that the adenohypophysis is concerned with many metabolic functions and reciprocal neuroendocrine relations accounts in large part for the complex mosaic pattern of endocrine and hypothalamic disorders which are char acteristic of acromegaly

(3) The changing secretory function of the sellar tumor which eventually ceases to be active and the increasing pressure atrophy of the undiseased portions of the adenohypophysis determine the general course of the malady This is characterized by a progressive but fluctuating intensity with alternating periods of exacerbation and remission which end in a terminal phase of adenohypophysial insufficiency

(4) The clinical coexistence of hyperactive and hypoactive adenohypophysial functional levels may be confusing but it is to be expected from what is known of the cytology and physiology of this gland

The unfolding clinical picture of this syndrome thus takes various forms which

Hochenegg[0 98 9], O Hirsch[100 101 10 103 104] and Cushing[83] have noted a certain retrogression in the cutaneous manifestations of this disease either during the spontaneous transition to the state of glandular insufficiency or in the immediate period following removal of the tumor The latter led Cushing to believe that a large part of the thickening and bogginess of the subcutaneous tissues must be due to an associated edema

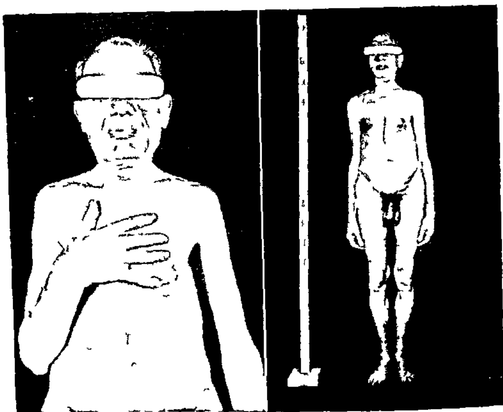


Fig 27 Acromegaly in an advanced state as a result of acidophilic adenoma Note wasting of musculature and subcutaneous tissue Compare with Fig 26 Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

The mucous membrane of the oral cavity is universally thickened The papillae of the tongue became hypertrophied Because of the marked hypertrophy of its muscular substance the tongue may protrude between the teeth in spite of the enlarged jaws Vocal articulation may be affected because of this increase in the weight and size of the tongue Often the larynx also is considerably enlarged, and the voice is deep, unless secondary gonadal atrophy supervenes

heat in the fingers and matutinal joint stiffness Severe arthritic or bone pain and profuse sweating both of which are more apt to be troublesome at night contribute to an enervating insomnia In women night sweats due to ovarian failure may complicate the clinical picture Ordinarily excessive perspiration occurs in acromegaly during periods of exacerbation of the pathological process and diminish or disappear during phases of quiescence

The headaches are in general of three distinct types of which there may be various combinations viz those due to an expanding sellar neoplasm or hyperplasia glandularis those induced by generalized increased intracranial pressure and those brought about by a mass of tenacious white mucus which is retained under pressure in the sphenoidal sinuses

The headaches due to the first of these causes usually occur early in the course of the disease inasmuch as the expanding lesion is confined initially to the rigid walled sella turcica By way of contrast it should be pointed out that benign interpeduncular and intradural tumors which affect the hypophysis only secondarily do not induce intracranial discomfort of any consequence until relatively late in the malady It is noteworthy however that the fossa may be greatly enlarged by the persistent pressure of a slowly growing tumor without significant discomfort even at the outset Ordinarily the headaches of hypophysial origin are severe persistent and bitemporal Sometimes they may subside spontaneously presumably because the pathological process in the gland has ceased to expand while the sella turcica and the dural capsule of the hypophysis have become distended adequately enough to accommodate their contents without undue tension or these headaches may disappear spontaneously because the tumor decompresses itself by herniating through the glandular capsule into an enlarged eroded sella Cushing s operative experience indicates that this type of headache is due for the most part to a stretching of the capsule of the gland inasmuch as splitting this tensely distended envelope results in immediate relief from pain

The second type of *headache is less well localized since it is related to a* generalized increase in intracranial pressure transmitted through partial obstruction of the ventricle It usually comes late in the disease and is associated with a papilledema which is superimposed on the primary optic atrophy characteristic of the earlier stages of the acromegalic syndrome

The third type of headache is frontal in position It is due to an increased intrasphenoidal pressure brought about by a mass of tenacious white mucus which is retained within the sphenoid cells because of partial occlusion of the sphenoidal foramina by a downward displacement of the sellar base It is not unusual for these headaches to be relieved spontaneously and intermittently by the periodic nasopharyngeal discharge of mucoid masses often blood tinged

The visual disturbances in acromegaly may be *precipitated in a more or less*

are determined in large measure by the extent to which and the order in which the foregoing factors are involved There is a basic pattern, however, which may be regarded as fairly typical

The onset of the disease usually is insidious, and its chronic course commonly is of long duration In the early stages of the disease either the victim or others of his acquaintance note a beginning change in the features The skin becomes coarse and thick the facial expression heavy and the forehead deeply furrowed The lips gradually thicken the ears and nose enlarge, and the dimensions of the hands and feet increase judging by the fit of rings gloves and shoes Occasionally before its true nature is revealed, the increased size of the hands and feet is thought to be due to edema The supraorbital ridges, the occipital protuberance and the malar bones protrude markedly The mandible is thrust forward in a characteristic fashion with consequent malocclusion Abnormal growth of the tongue may result in an embarrassing impediment to speech The skin pigmentation increases

At recurrent intervals in the syndrome the adenohypophysial dysfunction induces bouts of hyperthyroidism with nervousness, palpitation, tachycardia, tremor occasional exophthalmos and finally, myocardial embarrassment Later, however as the adenohypophysial lesion regresses in function, a state of myxedema supervenes in which the patient suffers from the cold, dryness of skin, absence of perspiration and an anemia which is recalcitrant to treatment Much the same sequence of events occurs in the realm of gonadal function Hypergenitalism characterized by an increase in the size of the external genitalia and heightened libidinous tendencies may occur at the onset but more often this phase is relatively transitory particularly in women It is succeeded by amenorrhea in the female impotence in the male, a progressive regression in the size of the external genitalia and anaphrodisia in both sexes

Although most of the foregoing acromegaloid changes are permanent there are circumstances in which a partial regression has been noted Alterations in the facial appearance and slight enlargement of the hands and feet are not infrequent in pregnant women and more or less complete recovery usually occurs in the post partum period Remarkable reversible acromegaloid changes have been noted post operatively by Cushing[83] Bailey and Cushing[39] have reported a fugitive type of acromegaly of short lived activity which is produced by mixed adenomas composed of acidophile and chromophobe cells They have assumed that degranulation of the chromophiles leads to their loss of overactive function, which is followed by a state of insufficiency and clinical regression

Acromegaly may manifest itself first through severe persistent or periodic headaches visual disorders and parasthesias of the face and extremities particularly of the hands The acroparasthesias often are associated with sensations of

defects are of important differential diagnostic significance The primary defect usually involves the color fields first the form fields are affected later Although there are variations and exceptions to the rules, the involvement ordinarily begins in the color boundaries of one upper temporal quadrant This is followed by more or less complete temporal hemichromatopsia and a beginning defect in the upper temporal form field The process gradually spreads downward until most of the temporal field is involved Post-operative restoration usually occurs in the reverse order

The history of bouts of excessive epistaxis appears repeatedly in accounts of the early phases of this malady whereas a later manifestation is anosmia due to local involvement of the cerebral nerves secondary to extrasellar extension of the adenohypophysial tumor Consequently anosmia is associated commonly with primary optic atrophy

Uncinate gyrus seizures characterized by gustatory and olfactory aurae with or without subsequent seizures are surprisingly common among Cushing s cases[83] In all such instances there was an interpeduncular extension of the hypophysial growth which doubtless pressed upon and consequently irritated the adjoining uncinate gyrus In a number of his patients the seizures were characterized by subjective gustatory and olfactory impressions associated with a dreamy unreal sensation but without subsequent epileptiform convulsions Cushing believes that the epileptiform tendencies without recognizable uncinate factors which he has noted in certain instances of primary hypophysial hypoplasia are due to the existent hypophysial insufficiency because there were no tumors to involve the uncinate gyrus secondarily

Direct or indirect involvement of the hypothalamus with its attendant symptoms of somnolence periodic or persistent polyuria and polyphagia generally comes relatively late in the course of events Although polyuria may develop early in the disease because of pressure atrophy of the posterior lobe it is said to disappear again with destruction of the adenohypophysis Polyuria and polyphagia may be associated also with the decreased sugar tolerance which usually appears somewhat early but may come late in the course of events This complication is characterized by hyperglycemia with or without significant glycosuria Eventually it gives way to an increased sugar tolerance during the late stages of adenohypophysial insufficiency In view of the recent importance attached to the hypothalamic origin of polyphagia it would be of interest to question whether or not the hypothalamus is concerned with the polyphagia of diabetes mellitus in cases other than acromegaly

Moderate adiposity is a consistent feature of active acromegaly upon which may be placed one of several interpretations The voracious hunger of some individuals afflicted with this disease has been attributed for the most part to

abrupt fashion with the appearance of homonymous hemianopsia or a slow but progressive loss of vision may herald the clinical onset of the disease Photophobia which is one of the occasional troublesome symptoms, is associated often with deep orbital discomfort and sensitiveness of the eyeballs to pressure Transient, recurrent episodes of diplopia also are encountered occasionally in the early stages of the disease On the other hand these visual disorders may not occur until relatively late in the course of the malady In any event they are obviously among the most important of the serious complications of this disease The most common of the visual disorders and obviously the most grave, are those manifesting interruption of the fibers of the optic nerve It has been determined by Cushing[93] *that the degree of involvement of these nerves bears* no direct relation to the size of the sella turcica The optic fibers apparently are more apt to suffer from an extrasellar mass than from a primary, adenohypophysial, acidophilic tumor Thus in many acromegalics one may encounter an enlarged sella without visual disturbances Chromophobe hypophysial adenomata, however, not infrequently cause profound involvement of the optic structures, possibly because they enlarge in the upward direction more rapidly than acidophilic tumors

Primary optic atrophy with some distortion *of the visual fields usually is* demonstrable in patients showing pronounced neighborhood symptoms Papilledema ordinarily is superimposed on the primary atrophy in the late stages, when the tumor has become large enough to induce increased intracranial pressure According to Cushing[84] the latter is due in the majority of instances to occlusion of the foramen of Monro with resultant hydrops of the lateral ventricles This complication usually provokes an abrupt onset of generalized pressure symptoms with an increase in headache and possibly vomiting The immediate cause of the papilledema is distension of the sheath of Schwalbe by persistent pressure through the cerebrospinal fluid That this is the mechanism may be gathered from case viii of Cushing s series *in which neuroretinal edema* did not occur during a phase of increased intracranial pressure because the optic nerve was completely enveloped in the tumor mass It appears also to some extent at least, that the amblyopia associated with primary atrophy represents a physiological block to light impulses rather than an actual destruction of the nerves Partial vision, including restoration of the visual fields not infrequently is restored promptly by operation even though there has been a brief preoperative period of total amaurosis

Bitemporal hemianopsia with a macular vertical meridian is not as common as many believe It is due to a bilateral upward extension of the tumor mass to the optic chiasm Homonymous defects are almost as frequent as bitemporal ones, and unilateral amblyopia may occur with little if any perimetric deviation in the opposite eye Cushing has emphasized that even tendencies toward temporal

in a patient whose symptoms are somewhat obscure presents the clinician with a diagnostic problem of some moment The differential diagnosis must be made preoperatively in order to determine upon the proper course of therapy For instance the acidophilic adenomata are quite sensitive to roentgen therapy whereas the chromophobe tumors are much less so[1 4] Aneurysm of the chiasmal area at times closely *resembles hypophysial adenoma* because it may *produce great* enlargement of the sella optic atrophy and visual field defects *Aneurysm may* be differentiated from other chiasmal tumors by x ray examination which may show a characteristic crescentic shadow from calcification in its wall or by arteriograms taken during the injection of thorotrast into the common carotid artery Naturally they call for a special form of therapy

The group of tumors consisting of chiasmal gliomas suprasellar meningiomas and cholesteatomas or chordomas should be recognized preoperatively so that there may be intelligent preparation for the special problems involved in their excision Any of these tumors by virtue of their anatomical location may be confused with acidophilic adenomata because they produce the same neighborhood signs and symptoms as a result of pressure upon the optic nerves and hypothalamus *With the exception of the craniopharyngiomas* which interfere with rather than accelerate growth and the chromophobe adenomata which affect adenohypophysial function by pressure atrophy the other masses usually do not induce hypophysial dysfunction Furthermore the craniopharyngiomas generally are cystic and give x ray evidence of calcification above the sella and the latter while *deformed is not often symmetrically distended as in the case of the hypophysial* adenomas Moreover these cysts tend to grow posterior to the chiasm in the direction of the third ventricle where their pressure produces an internal hydrocephalus with generalized increased intracranial pressure and choked discs instead of primary optic atrophy

The meningiomas in contrast to the craniopharyngiomas are found almost exclusively in adults although either tumor may occur in both age groups The meningiomas generally produce optic atrophy and bitemporal hemianopsia but the sella is likely to be normal in size or only slightly deformed The wide sellar expansion characteristic of adenomas ordinarily is not seen in connection with *gliomas of the optic chiasm and nerves cholesteatomas and chordomas* Although optic atrophy usually is present the visual field defects take unexpected forms and evidence of endocrine dysfunction rarely is well marked and usually limited to the hypothalamus

In the late phases of acromegaly the anatomical and radiological studies of *the skeleton reveal a diffuse dense sclerosis* which fills in the previously over expanded cancellous bone This secondary manifestation of hypophysial insufficiency contributes to the massive thickening of the skull and other parts of

the bouts of transient hyperthyroidism or diabetes mellitus which are encountered so commonly The association of a compelling polyphagia and obesity are consistent, however, with a hypothalamic disturbance, which could be secondary to the pressure effects of an expanding hypophysial tumor A third possibility is suggested by the observations of Lee[11], who found that the administration to rats of an adenohypophysial growth hormone increased the appetite and the voluntary food consumption and promoted weight gain by an increased deposition of body protein The fact that hormones such as estrogens, progesterone and pitressin, are known to affect the function of certain hypothalamic centers suggests that the second and third of these possibilities may have a common denominator, i e the growth hormone elicits its effect on appetite and body weight by way of the hypothalamus

Differential Diagnosis

The nature of the disease process in the fully developed syndrome is identified easily by the general appearance of the patient and confirmed by x ray examination of the sella turcica sinuses mandible, general configuration of the skull and terminal phalanges Diagnostic difficulties are more apt to arise in the recognition of the so called fugitive cases and of the very early or very late phases of this disease

The early stages of acromegaly frequently are confused with other conditions Rheumatoid pains may suggest arthritis or in the absence of objective physical findings the combination of vague muscle and bone pains, nervousness, weakness and insomnia often lead to a diagnosis of hypochondriasis The significance of the headache is quite apt to be misinterpreted The acroparesthesias and burning sensations of the hands may suggest syringomyelia Early disturbances in gonadal function particularly with the onset of amenorrhea are especially misleading The relatively frequent complication of acromegaly by hyperthyroidism, diabetes mellitus diabetes insipidus and the hypothalamic syndrome, which is characterized by polyphagia obesity and hypersomnolence, may direct attention for a time from the primary hypophysial disease to one or more of these secondary clinical disorders The cutaneous hyperpigmentation weakness vague gastrointestinal symptoms and hypotension may suggest an early phase of Addison s disease The otolaryngologist not too rarely has treated an early case of acromegaly for chronic upper respiratory disease and sinus disease without recognizing the significance of the periodic, often blood tinged, nasopharyngeal, mucoid discharges The ophthalmologist who is confronted by an unexplained diplopia, should search for homonymous hemichromatopsia since it precedes the development of a full blown hemianopsia

The discovery of a tumor in the region of the sella with incipient optic atrophy

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In the late phases of acromegaly the anatomical and radiological studies of the skeleton reveal a diffuse dense sclerosis which fills in the previously over expanded cancellous bone This secondary manifestation of hypophysial insufficiency contributes to the massive thickening of the skull and other parts of

the skeleton As a result of these late changes acromegaly may have to be differentiated occasionally from leontiasis ossea, Paget s disease and Marie s hypertrophic pulmonary osteoarthropathy In the latter condition the skull remains unaffected although the nose may appear prominent, the finger tips are clubbed, and the hands and feet increase but slightly in size The kyphosis is thoracolumbar whereas in acromegaly it is cervicodorsal The enlargement of the hands and feet in osteoarthropathy is, on rare occasions sufficient to cause some temporary confusion with acromegaly but the rest of the clinical picture should distinguish the one from the other Paget s osteitis deformans scarcely is likely to be mistaken for acromegaly The cranium is enlarged, chiefly in circumference the long bones are pathologically bowed, and the asymmetrical skeletal changes show characteristic roentgen changes in the skull and long bones

Treatment

The type of therapy which is instituted in acromegaly, is dictated in large measure by considerations which arise in the individual case There are three therapeutic procedures which are available viz x ray therapy, surgery and use of hormones

X Ray Therapy —In 1909 Gramegna reported the first case of acromegaly with hypophysial tumor to be treated by roentgen rays[110] Since that time the majority of reports have indicated that irradiation is of much benefit in many cases[108 109 110 111 11 113 114 115 116 117 118 119] Most of these observers favor irradiation as the method of choice in the treatment of hypophysial adenomata uncomplicated by advanced involvement of the optic chiasm and nerves The ideal patient for roentgen therapy is one who has endocrine disturbances and possibly a slight enlargement of the sella turcica but no visual disorders It is patently unwise to await development of the latter before instituting treatment

Heinismann and Czerny[109] confirmed by Dyke and Hare[1 0] have pointed out that the acidophile adenomas in acromegaly respond to irradiation better than the chromophobe type Judging from the various reports roentgen therapy has induced improvement in visual acuity, headache and secondary endocrine disorders for a period of from 1 to 7 years or more in many patients Even if vision is unimproved by x ray therapy its progressive deterioration may be halted for many years[109] There is general agreement particularly emphasized by Dott Bailey and Cushing[113] that roentgenotherapy should be followed by carefully controlled and frequent perimetric observations, and that surgical intervention is indicated, if vision continues to diminish

Radiation apparently causes a temporary regression of vision for 24 hours after the treatment is administered[1 9] This may be due to post radiation edema of the

tumor and adjacent brain tissue since the vision usually begins to improve within 12 to 24 hours after these initial undesirable effects are noted

Failure to achieve improvement with roentgenotherapy may be due to an irreparably damaged optic chiasm and nerves or the hypophysial tumor may be largely cystic and consequently unresponsive

The amount of radiation needed appears to vary from case to case Dyke and Hare[2] have noted improvement in vision headache lethargy and other general symptoms after several hundred roentgen units Other cases did not respond until 2 000 r to 4 000 r had been given They suggest therefore that therapy be continued provided that vision is not too greatly diminished until the patient has received three or four series of treatments each of which consists of a total of 1 400 r to each of three portals

Surgery — Endocrine disorders alone without evidence of pressure upon the optic nerves optic chiasm or the hypothalamic structures rarely if ever justify surgery of the hypophysis Loss of vision from optic atrophy and symptoms of increased intracranial pressure produced by adenomas which extend backward and upward constitute the only clear cut indications for reducing the size of the tumor or for its complete removal [6]

The sella turcica was approached surgically first through the nasal accessory sinuses since the deeper of these structures lies beneath the hypophysial fossa In 1906 Schloffer operated upon a hypophysial tumor through an extensive resection of the endonasal and postnasal structures including the ethmoid and sphenoid cells This original procedure was employed and subjected to simplifying modifications by Hochenegg [9] and von Eiselsberg[1] [1] in 1907 by Kanavel [1] Hirsch [9] Kocher[1] and Lecene[1] in 1909 and by Halstead in 1910 An account of the degree to which Cushing perfected this operative approach may be gathered from his monograph in 1912 and his two subsequent reports in 1914[1] [5] and 1922[1]

In Hochenegg s first two cases of acromegaly and in one of O Hirsch s patients there were unmistakable signs of post operative subjective and objective improvement The rheumatoid pains disappeared the acra decreased in size the menses were restored and recurred at regular intervals the skin became softer and the excessive hairiness regressed These observations have been confirmed repeatedly especially by Cushing

According to Horrax the operation of choice at this time is the transfrontal intracranial approach Modern advances in technical skill have lowered the operative mortality of this procedure from its previously prohibitive levels [3] [11] [132] to less than 5 per cent The hypophysial tumor is more accessible it can be evacuated more completely and vision is more likely to be improved or restored by this method than by the transphenoidal technic Cushing[1] [9] states whereas

37 per cent of the patients after transphenoidal operations and 42 per cent after transfrontal operations showed considerable or marked improvement in vision, only 9 per cent of the transphenoidal operations in contrast to 21 per cent of the transfrontal operations were followed by restoration of the visual field and acuity essentially to normal

Hormone Therapy — Endocrine therapy in acromegaly has two aims, either to induce regression of the acidophilic pathologic process, or to correct the endocrine disorders secondary to adenohypophysial insufficiency The former, which still is wholly in its experimental stage is based on experimental evidence, which indicates that the sex hormones have a depressant effect upon certain aspects of adenohypophysial function It is difficult however, to envisage success in this connection, where a growing tumor is concerned whereas an uncomplicated hyperplasia of the acidophiles might be a more logical target for this form of therapy

Substitution therapy for the repair of disabilities resulting from adenohypophysial insufficiency is also in its developmental stages, principally because a clinically satisfactory extract of all the principles of the adenohypophysis is not yet available Contrary to the therapeutic indications in Simmonds disease such an extract should contain all factors except that concerned with growth, if it is to be used in the treatment of this phase of acromegaly Whether or not this omission would limit or in some way modify the clinical activity of the extract remains to be seen Nevertheless much can be done to obviate the secondary manifestations of genital adrenal thyroid and posterior lobe deficiencies Nature herself fortuitously has taken a hand in the management of the diabetes mellitus, inasmuch as the advent of adenohypophysial insufficiency generally heralds a change from a state of decreased to one of increased carbohydrate tolerance The other deficiencies are treated in the orthodox fashion with the possible exception of that of the thyroid It has been pointed out[113,114,115] that thyroid therapv in such circumstances may precipitate an acute attack of adrenal insufficiency by virtue of the sudden excretion of sodium chloride and water in an individual whose adrenal cortex already is significantly atrophied The likelihood of such an accident in a patient who needs thyroid therapy furnishes a clear cut indication for the combined administration of thyroid sodium chloride and possibly adrenocortical extract

GIANTISM

Definition

Giantism may be defined as an anomaly of skeletal growth characterized principally by a stature which is considerably in excess of the average measure

ments of individuals of the same race Associated with this general symmetrical *overgrowth of the body there is usually a decided impairment in sexual functions* and persistence of ununited epiphyses

Biological Significance

It is customary to refer to the various bony skeletal findings in giantism as pathognomonic of this disease but Launois and Roy[136] believe that these are merely exaggerations of the conditions found in normal men who are unusually tall Thus in order to understand the atypical growth of giants it is essential to recall the laws and progress of normal growth To merit the title of giant it is not sufficient for an individual merely to be extraordinarily tall Of two persons of equal height one may be a giant and the other a normal but unusually tall individual There are no sharply defined differences between the normally tall man and the giant The one merges into the other through a wide variety of in between types Individual variability is almost endless This applies to the height as well as to the proportions of the various parts of the body The body type varies with race country diet quantity and form of muscular activity etc

Launois and Roy have concluded that the same laws which govern the growth of so-called normal individuals determine the type of overgrowth which occurs in giantism[136] They find for the giant as did Godin[137] for the normal that the growth drive continues at irregular intervals which are interrupted by periods of relative slowing

The genetic factors which Stockard[3, 139] observed and demonstrated for the pathogenesis of acromegaly in various breeds of dogs are equally applicable to the disorder of growth in giantism It is likely that in giantism, just as in acromegaly the individual inherits a constitution, which is expressed in terms of a genetically determined defect in the structure and function of the adenohypophysis Eunuchoidal characteristics may or may not be a feature of this constitutional deviation from the average normal growth, a matter which has been discussed recently by Mansbacher[140] The latter has suggested that the eunuchoidism may be a familial characteristic in much the same way as the giantism with which it is associated often

Incidence

Giantism *is a relatively rare condition* Its incidence *apparently is greater* in the male than in the female Of 14 accurately studied cases which were reviewed by Hutchinson[141, 142] 10 were in males Examples of familial giantism may be more common than the number of recorded cases indicated In his studies

of inheritance of stature Davenport[147] has collected data on a few families distinguished by unusually tall members. One reason for the dearth of statistics on this phase of the subject may be the difficulty in differentiating the various clinical types of linear overgrowth. Most giants exhibit infantilistic or eunuchoid characteristics which must be differentiated from the gonadal hypoplasia associated with so called secondary eunuchoidal giantism.

Pathology

The pathological material, upon which studies of giantism have been based, is limited in amount but has been examined carefully. Hutchinson[141, 14] reported 3 cases in all of which the adenohypophysis was found to be considerably enlarged by a neoplasm. Launois and Roy[146] collected a larger series of autopsied cases which disclosed that an adenoma of the adenohypophysis was present in all true giants whereas only hyperplastic enlargement of the gland occurred in other instances of unusually tall stature, e.g., eunuchoidal overgrowth. The available evidence indicates that all such adenohypophysial tumors consist of acidophilic cells, and that the acidophiles are affected also in cases of hyperplastic enlargement of this gland. Consequently it is believed that the pathological process which induces giantism is responsible also for the development of acromegaly[1, 6, 141, 14, 144, 145]. As was noted elsewhere in this chapter, the acidophilic tumor probably induces giantism if it affects the growth of an individual prior to union of the epiphyses, and acromegaly results if the adenoma becomes active after epiphyseal union. A variable mixture of these two clinical states occurs, if the pathological process spans the period of adolescence and adulthood.

These conclusions are of interest in view of Rasmussen's observations[148], which fail to show any correlation between the percentage of acidophiles and stature. Roessle[14, 14], Petersilie[149] and Rasmussen[148] have found, however, that there is a distinct positive correlation between body length and the weight of the entire hypophysis. Rasmussen's studies[148] have disclosed also a moderate degree of positive correlation between stature and the weight of the pars distalis.

Clinical Course

Since the growth curve of the giant is essentially an exaggeration of the normal according to Launois and Roy[1, 6], it is not surprising that the abnormal growth of giantism ordinarily begins during the periods of accelerated growth in normal children. Although the earliest evidence of giantism is encountered during the first year of life, Biedl reported that most cases become clinically apparent late in childhood, usually at the time of puberty[150]. A classical example of the infant

giant occurred in the Alton boy who began to grow excessively soon after birth[151] By the time he was 2 years of age his height arrested attention and at 9 he measured over 6 feet in height By his twelfth birthday he had grown to almost 7 feet and at 18 he topped the extraordinary height of 8 feet 3 inches The stature of verified cases on record varies from 7 feet 6 inches to 8 feet 6 inches in the case of the famous giant in Trinity College Dublin A fantastic height of 9 feet or more has been claimed for various human giants but Roessle states that these are not authentic measurements[1 7 148]

An extensive survey of approximately 100 cases of giantism indicates that the life of these unfortunates is short and far from merry Dana has found[16] that the average length of life is 21 3 years although some of these individuals lived beyond 50 years of age The end of life generally is heralded by a diminishing vitality and the immediate cause of death usually is a mild intercurrent infection which in other circumstances would be of no clinical significance

Launois and Roy[138] point out that the epiphyses of giants remain ununited many years beyond the period of normal ossification The giant continues to grow in height as long as this prepuberal condition of the growth cartilages persists The clinical stigmata of acromegaly generally are inconspicuous in the growing giant but emerge as part of the syndrome when the growth period has terminated *because the fundamental pathology of both diseases is the same* Thus a considerable proportion of giants become acromegalic in adult life

Physical Signs and Symptoms

Contrary to popular belief giants in size are not supermen in strength Cases *have been reported in which unusual physical prowess was a passing phase early* in the course of this malady For the most part however giants are physically weak and have difficulty in supporting their weight safely[141 142] A survey of the *literature also discloses that the majority of giants are indolent and fail to develop* an intelligence much beyond that of a child s and failure of memory is a common complaint Hutchinson [15] believes that giants are feeble minded because of their disease *It is also* possible that their freakish overgrowth interferes seriously with their social and psychological adjustments and their progress in educational pursuits

Most giants suffer from a decided impairment in sexual functions but this is not invariably characteristic Entirely normal or even exaggerated sexual development in the early phases of this disease is not inconsistent with the diagnosis Although many of these individuals have been urged into wedlock by business managers in the belief that they would reproduce their kind their marriages have been few and largely infertile The external genitalia have been found to be

markedly underdeveloped in most of the cases in which trustworthy observations have been made In Hutchinson s case of female giantism the uterus was infantile, the ovaries rudimentary and the clitoris markedly hypertrophied

The abnormal stature of giantism is associated with certain characteristic bony changes, among the most prominent of which is the overgrowth of cancellous bone throughout the skeleton The mastoid cells and sinuses become extraordinarily large in size and the squamous portion of the temporal bone is hyperpneumatized The broad diploe between the inner and outer tables of the cranium are unusually prominent The characteristic physiognomy and prognathism of the giant is due in large part to the facial bones and particularly, to the mandible, which is hyperpneumatized

Relatively narrow shoulders have been encountered in many of the larger giants Thus the height span relations are affected and become an important index to a characteristic feature of giantism The span usually measures less than the total height because of the narrow width of the shoulders During his twelfth year the Alton giant grew 11 cm in height, increased 11 5 cm in arm span and 13 cm in circumference at the level of his iliac crest, but the length of the clavicles remained stationary[153]

The abnormally long arms hang beside the giant in simian fashion Giants have enormous feet and characteristically enlarged, spade shaped hands Both jaws are hugely developed the cheek bones are extremely prominent, and the supraorbital ridges project to such a degree that they resemble those of an anthropoid ape

Differential Diagnosis

Constitutional Statural Overgrowth — The excessive growth of giantism differs from the normal physiological development only in that the length of the extremities and body height and the size of the viscera are considerably in excess of the average measurements peculiar to the race of the individual concerned A height of over 6 feet is not considered gigantic among members of the Scandinavian peoples, whereas the same stature in an individual of one of the Latin races might well raise the question of hypophysial dysfunction In addition to race height is influenced also to a considerable degree by genetic factors Excessive stature may be essentially an inherited characteristic which is dependent upon genetic constitution In such instances neither the skeleton nor the other organs of the body exhibit any evidence of disease (Fig 28) It should be noted, however, that a genetically determined tall stature in one or both parents does not rule out the possibility of a pathological overgrowth, if one of the offspring also develops excessively In such circumstances the possibility of abnormal growth

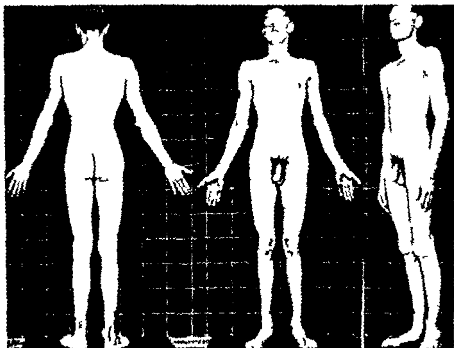


FIG 8 Constitutional statural overgrowth Age 18 Sella turcica small measuring 5 x 7 mm with partial convergence of clinoid processes Bones of hands and wrists are unusually large and the ulnar epiphyses are not completely fused No family history of giantism but one sister aged 20 grew 2 inches within a few months after giving birth to a baby and a paternal aunt grew several inches rapidly after she was 20 years of age Father is 68 inches t ll mother 61 inches Patient weighs 163 pounds and is 77½ inches in height Lower skeletal segment 42⅞ inches Upper skeletal segment 34⅝ inches Arm span 79½ inches These eunuchoidal skeletal measurements are associated with virtual absence of body hair transverse pubescence poor libido and unusually small prostate It is difficult to explain the normal size of the external genitalia unless one assumes that the development of the penis and gonads is a genetic variation which is not an expression of the state of gonadal function Note prominent mandible which has not resulted in malocclusion in this case Reproduced through the courtesy of E Kost Shelton M D

should be investigated whenever children or adolescents are oversized for their age or begin growing at too rapid a pace

Eunuchoidal Giantism — Statural overgrowth associated with primary gonadal hypoplasia must be differentiated from true giantism which also is characterized commonly by undeveloped genital organs Both conditions exhibit a somewhat similar general appearance and skeletal configuration, but there are

several distinguishing features which aid in the differential diagnosis (Fig. 29). X-ray examination of the phalanges of the eunuchoidal giant shows a more slender, less massive bone structure than is characteristic of the true giant. Furthermore, the skeletal measurements are more disproportionate in the eunuchoidal individual, whose span may be considerably in excess of his total height, whereas the span of the true giant ordinarily is equal to, or shorter than, his total height. The latter may be attributed to the failure of his clavicles to grow in proportion to the rest of the skeleton. This results in narrow shoulders and shortens the span, which might exceed the total height otherwise. Finally, roentgen study of the sella turcica may disclose a small, fully enclosed bony structure in the case of the eunuchoid giant, whereas an enlarged, eroded sella turcica is found ordinarily in the true giant. It should be emphasized, however, that the absence of a pathologically altered sella turcica does not necessarily distinguish the one from the other in puzzling diagnostic problems. The author has observed one case and Hurxthal and Horrax[154] have reported another in which the development of giantism was traced to a verified hypophysial tumor, although roentgen evidence of an enlarged sella turcica was lacking. A pneumoventriculogram may disclose the diagnosis in these circumstances because the expanding tumor, which has herniated through a frail diaphragma sellae, often produces a filling defect in, and a displacement of, the ventricular system. Involvement of the optic chiasm or optic nerves occurs ordinarily in such cases and aids thus in the differential diagnosis. Delayed union of the epiphyses occurs in both types of statural overgrowth under consideration, so that this finding does not help in differentiating these conditions.

Statural Overgrowth in Exophthalmic Goiter.—The rate of growth is accelerated in juvenile and adolescent individuals who are afflicted with exophthalmic goiter during the period of their active growth[155,156,157,158,159,160,161]. Consequently such individuals are taller than average for their age, sex and race. The duration of this accelerated rate of growth is not a factor in the final unusual height which is attained inasmuch as the epiphyses unite at the proper time. There should be no difficulty in the differential diagnosis of this condition from that of true giantism, even though a height in excess of 6 feet may be attained rapidly in occasional instances. As a matter of fact the clinical problem, with which one is confronted in such cases, stems generally from anxiety over the unusual rate of growth in a child that lacks emotional stability.

Urinary Excretion of Hormones in Relation to Problems of Growth.—Individuals exhibiting eunuchoidal giantism due to primary gonadal failure excrete an increased amount of FSH and a decreased amount of the estrogenic and androgenic hormones in the urine. The neutral 17-ketosteroid excretion may be within normal limits or moderately decreased. The author is

Fig 39 Eunuchoidal giantism in a 15 year old boy Note disproportionate skeletal measurements cubitus valgus extreme hypoplasia of external genitalia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital.



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occur in the male Tumors of the sex glands have been reported in both sexes but tumors of the pineal are sex linked and occur exclusively in the male

Treatment

Of the various forms of therapy which have been suggested for the control of excessive growth in primary hypophysial giantism none is advocated with enthusiasm Horrax[1] states that surgical removal of the acidophilic tumor which is associated commonly with this condition is indicated only rarely since visual disturbances are infrequent and roentgenotherapy often arrests the growth of expanding acidophile tumors of the adenohypophysis Surgery appears to be the method of choice only when radiation fails to produce significant improvement in the eyesight of individuals who develop optic atrophy

Androgenic and estrogenic hormone therapy has been advocated in recent years[63,164] for the control of eunuchoidal giantism in the belief that these substances either depress adenohypophysial function or initiate rapid union of the epiphyses Although apparent success has been achieved in a few cases it is difficult to judge the accuracy of such observations inasmuch as the rate and extent of statural growth may vary spontaneously and abruptly in a given individual without reference to the therapy which has been administered It was indicated in a previous section of this chapter that the androgens of the adrenal cortex may be involved in initiating union of the epiphyses and cessation of growth Whether or not the androgenic corticosteroids behave differently in this respect from the androgens derived from the testes is still to be determined If substantiated the information may have significant therapeutic implications

The discussion of hormone therapy in acromegaly contains a statement of the present views on that phase of the subject as it relates to acidophilic tumors and hyperplasia of the adenohypophysis Because of the similarity in pathology presumably much the same indications and limitations apply to the use of this form of therapy in giantism

Dwarfism

Definition

A dwarf is an individual whose physical dimensions are considerably below those characteristic of his age group sex and race The term *dwarfism* per se refers to the diminutive stature and may be due to one or more of many causes such as genetic variation secondary to germinal defects adenohypophysial deficiency secondary to various types of tumor in the hypothalamo hypophysial area congenital or acquired hypothyroidism hypophysial neighborhood or sys

not aware of similar studies on hypophysial giants Klinefelter, Albright and Griswold[16] have studied the FSH excretion in patients with acromegaly, however Since these two syndromes are associated with the same pathological lesion of the adenohypophysis it is of interest to note that the excretion of FSH may be normal decreased or elevated in acromegaly Presumably the level of excretion depends in large measure on the extent to which the expanding acidophilic tumor damages the basophilic cells through pressure atrophy In one case of acromegaly which occurred during the menopause, the FSH excretion was found to be increased[16] In the author s experience the 17 ketosteroid excretion is normal, decreased or virtually absent in acromegaly The amount of excretion parallels closely the clinical activity of the acromegalic process The 17 ketosteroid excretion is normal in early well established cases, decreased in moderately advanced states and absent in individuals who show clinical evidence of hypophysial deficiencies secondary to local destruction of the functional adenohypophysial parenchyma

Rare Childhood Disorders of Growth and Sexual Development —The hypophysial type of overgrowth is not characterized by sexual precocity, which ordinarily signifies disease of the gonads, of the adrenal cortex or of the pineal body, nor do these non hypophysial types of overgrowth end in giantism This comparatively rare group of childhood disorders of growth and sexual development are included under the general heading of *macrogenitosomia praecox* As the name indicates the salient features of these conditions are precocious skeletal somatic and genital development Ossification centers appear too early bone development is advanced correspondingly, and epiphyseal union takes place prematurely Although such children seem remarkably overgrown when they come under observation they do not exhibit giantism in adult life As a matter of fact, the reverse is true of those who survive to adulthood Such children are dwarfed because premature closure of the epiphyses and early maturation of the reproductive system result in cessation of longitudinal growth long before it should occur normally

More often these patients do not survive their childhood, because the pathological condition responsible for their precocious development is a malignant tumor of the adrenal cortex, pineal or gonads Friedgood and Gargill[1] have observed an instance of malignant adrenocortical tumor in an 8 year old girl, who showed skeletal and somatic precocity and menstruated for six months before she developed outspoken virilism associated with amenorrhoea The condition is found more commonly in female children who develop the symptoms and signs of virilism Boys who are affected by a similar neoplasm develop premature over masculinization Neoplasms of the gonads induce menstruation at an early age in the female whereas priapism and spermatogenesis

it is generally believed that the Lorain dwarf has the body proportions of an adult in miniature There is nothing in the Lorain Faneau de la Cour treatise to justify *this interpretation Actually what they stated was that their tuberculous patients* both male and female were juvenile in appearance and persistently infantile in somatic and sexual development despite advancing years *They reported* that a fragile body habitus spindly limbs small bones and weakness were the outstanding characteristics of an arrested somatic development which affected the whole body rather than any special part of it The teeth of these adult dwarfs were mostly of the first dentition The breasts of the women were undeveloped they had little or no axillary or pubic hair and although their external genitalia were of the female type they were immaturely developed In the absence of autopsy or x ray data Faneau de la Cour surmised that their epiphyses were ununited a remarkably accurate deduction in the light of subsequent more modern studies *The secondary sexual characteristics of the tuberculous males affected by* this condition were predominantly feminism and the development of their external genitalia seriously arrested *They had broad hips* absence of hair on face and thorax long eyelashes prominent breasts fine silky hair of the head small testes and an infantile penis For example the development of the external genitalia in one of their cases a man of 25 was equivalent to that of a child of 8 or 9 years

It would scarcely serve any useful purpose to recapitulate the tedious academic arguments which cluttered the literature on this subject subsequent to the Lorain Faneau de la Cour article Some of it may be gotten from papers by Brissaud and Meige and Bauer[16] who contributed to the controversies regarding relative body proportions and etiological factors in infantilism In 1908 Levi described *an instance of infantilistic dwarfism in which an hypophysial tumor was obviously* the primary pathological lesion[1, 9, 17a, 12] The literature which accumulated after this report refers repeatedly to the Lorain Levi syndrome So far as this writer can determine the clinical characteristics of these two groups of infantilistic dwarfs are essentially identical From this viewpoint there appears to be some justification for the syndrome s name Etiologically however they are unrelated the Lorain Faneau de la Cour syndrome having been found in association with pulmonary tuberculosis whereas Levi s case was due to a destructive lesion of the adenohypophysis

The most widely quoted classification of dwarfs was introduced by von Hansemann[22] in 1902 *His disproportioned* dwarfs included the rachitic achondroplastic *kyphoscoliotic and cretinoid forms and the well proportioned dwarfs* were subdivided into primordial and infantile types The primordial dwarfs are *of normal intelligence and in the absence of evidence to the contrary may be con*sidered as examples of a disordered growth which results from defects in germ plasm They are abnormally small at birth and although their rate of growth

temic infections severe nutritional deficiencies and chronic heart disease acquired congenitally or in infancy The association of gonadal hypoplasia with dwarfism of whatever cause is termed *infantilism*

Hypophysial dwarfism is a chronic endocrine or neuroendocrine disorder which is characterized in the large majority of cases by adenohypophysial pathology during the period of somatic development This form of dwarfism is recognized clinically by a well proportioned diminutive infantile stature and a correspondingly small head with child like features which acquire an incon gruous wizened oldish expression relatively early in life Union of the epiph yses is delayed markedly or never occurs, but it may be encountered in those hypophysial dwarfs who mature sexually in rare instances Among the various infantile characteristics which persist in hypophysial dwarfs, is under development or atrophy of the genital apparatus and emotional immaturity *Hypophysial infantilism* is characterized furthermore, by certain biochemical and biological changes including markedly reduced or absent urinary excretion of neutral 17 ketosteroids and urinary gonadotropin abnormal sensitivity to injec tions of insulin and an increased tolerance for carbohydrates

Historical Background

Numerous examples of skeletal dwarfism associated with gonadal hypoplasia have been recorded in the medical literature Considerable confusion has re sulted from attempts to separate them into well defined clinical syndromes, be cause in many instances etiological factors have been essentially obscure, dis tinctions between groups of cases are not hard and fast and intermediate forms of this disorder have defied all efforts at logical classification Particularly dif ficult has been the task of differentiating between hypophysial dwarfism and the stunted stature which appears to be due to a genetic modification of growth based on germinal defects To further complicate the situation there have been numer ous relatively unimportant and involved academic controversies on matters of terminology Reference to Falta s involved analysis of the arguments and counter arguments on various aspects of infantilism gives some idea of this unsat isfactory state of affairs[165]

In 1871 Lorain and Faneau de la Cour[166] described a group of tuberculous individuals in whom they noted arrested skeletal and genital development They termed the condition infantilism Unfortunately a misquoted version of their paper was incorporated into the literature on dwarfism and infantilism, and Lorain s name was identified with a syndrome which was not precisely what he and his pupil described The confusion in terminology and the pointless academic discussions which have centered about the error are a matter of record Briefly

it is generally believed that the Lorain dwarf has the body proportions of an adult in miniature. There is nothing in the Lorain-Faneau de la Cour treatise to justify this interpretation. Actually what they stated was that their tuberculous patients, both male and female, were juvenile in appearance and persistently infantile in somatic and sexual development despite advancing years. They reported that a fragile body habitus, spindly limbs, small bones and weakness were the outstanding characteristics of an arrested somatic development which affected the whole body rather than any special part of it. The teeth of these adult dwarfs were mostly of the first dentition. The breasts of the women were undeveloped; they had little or no axillary or pubic hair, and although their external genitalia were of the female type, they were immaturely developed. In the absence of autopsy or x-ray data, Faneau de la Cour surmised that their epiphyses were ununited, a remarkably accurate deduction in the light of subsequent more modern studies. The secondary sexual characteristics of the tuberculous males affected by this condition were predominantly feminism and the development of their external genitalia seriously arrested. They had broad hips, absence of hair on face and thorax, long eyelashes, prominent breasts, fine silky hair of the head, small testes and an infantile penis. For example the development of the external genitalia in one of their cases, a man of 25, was equivalent to that of a child of 8 or 9 years.

It would scarcely serve any useful purpose to recapitulate the tedious academic arguments which cluttered the literature on this subject subsequent to the Lorain-Faneau de la Cour article. Some of it may be gotten from papers by Brissaud[167] and Meige and Bauer[168] who contributed to the controversies regarding relative body proportions and etiological factors in infantilism. In 1908 Levi described an instance of infantilistic dwarfism in which an hypophysial tumor was obviously the primary pathological lesion[16, 170, 171]. The literature which accumulated after this report refers repeatedly to the Lorain-Levi syndrome. So far as this writer can determine, the clinical characteristics of these two groups of infantilistic dwarfs are essentially identical. From this viewpoint there appears to be some justification for the syndrome's name. Etiologically, however, they are unrelated, the Lorain-Faneau de la Cour syndrome having been found in association with pulmonary tuberculosis, whereas Levi's case was due to a destructive lesion of the adenohypophysis.

The most widely quoted classification of dwarfs was introduced by von Hansemann[17] in 1902. His "disproportioned" dwarfs included the rachitic, achondroplastic, kyphoscoliotic and cretinoid forms, and the "well-proportioned" dwarfs were subdivided into primordial and infantile types. The primordial dwarfs are of normal intelligence and in the absence of evidence to the contrary may be considered as examples of a disordered growth which results from defects in germ plasm. They are abnormally small at birth, and although their rate of growth

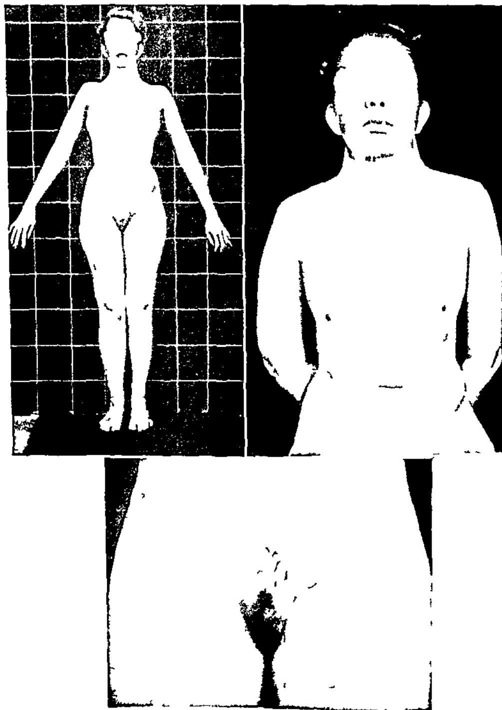


FIG 30 Turner's syndrome in a 25 year old girl with primary amenorrhoea Note webbed neck absence of breast development and hypoplasia of genitalia Compare with similar case in Fig 31 in which dwarfism is a factor Courtesy of E Kost Shelton M D

remains inhibited the epiphyses unite at the usual time They mature sexually and develop secondary sexual characteristics at puberty at the expected time Many of these individuals are capable of procreation and may have normal children The infantile dwarfs who are brought about by adenohypophysial deficiency are normal in size or somewhat smaller than normal at birth At some later time usually in early childhood their growth ceases entirely or is retarded so that the rate of growth is interfered with seriously The epiphyses remain ununited indefinitely development of the primary and secondary sexual characteristics either fails entirely or is significantly impaired the intellect sometimes remains puerile but is not defective Von Hansemann s infantile dwarf obviously is identical with Gilford s[1 3] asexual ateleiotic dwarf and with the Paltauf type of dwarfism[174] whereas von Hansemann s primordial dwarf corresponds to Gilford s sexual ateleiotic dwarf[1] Sternberg[1 6] who believed that infantilistic dwarfism sometimes is due to primary gonadal hypoplasia further subdivided von Hansemann s class of infantile dwarfs into hypophysial and hypoplastic gonadal types The association of stunted growth with agenesis or arrested development of the ovaries has been recognized pathologically and described by Olivet[177] Sellheim[1 8] Randerath[17] Schurmann[1] Pela[181] Priesel[8] Rossle[153] Goldwasser[183] Tronci[185] Sharpey Shafer[1 6] and Wilkins and Fleischmann[187] Various clinical aspects of this syndrome were reported in detail by Turner[1 8] Varney Kenyon and Koch[9] Albright Fraser and Smith[189] Schneider and McCullagh[1] and Wilkins and Fleischmann[18] Sometimes it is called Turner s syndrome (Figs 30 and 31) It is characterized by a dwarfed stature and retarded or absent sexual development in association with high titers of urinary gonadotropin and an abnormally low excretion of androgens and estrogens The external and internal genitalia are infantile development of the breasts is lacking and there are small to moderate amounts of axillary and pubic hair in spite of a complete lack of the other so called secondary sex characteristics Menses occur only infrequently and usually not at all depending on the extent to which the ovarian development is arrested Congenital anomalies such as webbing of the neck and short neck in association with abnormalities and fusion of the cervical vertebrae and cervical spina bifida are encountered not infrequently Other congenital anomalies which have been noted include squint bilateral ptosis bilateral cataracts tubular vision lack of retinal pigment deafness and mental retardation Individuals who comprise this group may or may not be obese and examination of their photographs[18] discloses that usually they have the body proportions of a child although eunuchoidal skeletal measurements have been observed[87 19 1] It is thought that the association of growth and ovarian defects may be of genetic rather than of physiological significance[187 9 19] The differentiation of these cases from those of hypophysial origin has been undertaken in a subsequent section of

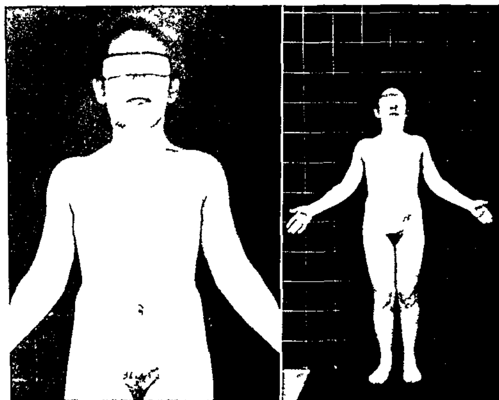


Fig 31 Turner's syndrome in a 19 year old girl with primary amenorrhoea Note webbed neck absence of breast development cubitus valgus and dwarfism Reproduced through the courtesy of E Kost Shelton M D

this chapter In a recent critical review of the many clinical aspects of dwarfing Shelton[193] has suggested the following classification of dwarfism and infantilism from a practical viewpoint

(1) Inherent or constitutional factors as in so called primordial dwarfism and in normal small statured persons
(2) Congenital disturbances of the skeleton as in achondroplasia mongolism and micromelic dwarfism
(3) Anomalies of the circulatory and urinary systems as in congenital heart and kidney disease angioplastic infantilism and renal rickets
(4) Disturbances of nutrition
  (a) Inadequate food vitamin and mineral intake, as in slow starvation rickets and other deficiency diseases
  (b) Inadequate absorption of the building essentials because of disturbances

of the gastric intestinal and pancreatic enzymes as in hypochlorhydria celiac disease *refractory rickets and intestinal nematodes*

(c) Inadequate utilization or deposition of the essential elements because of various metabolic and endocrine disorders as hypothyroidism hypopituitarism and diabetes mellitus

(5) Chronic infectious disorders as in tuberculosis and syphilis

Pathology

There are relatively few recorded data of autopsies on dwarfs So far as this writer can ascertain all such observations have been made on infantilistic dwarfs *none are available for the so-called primordial dwarf The adenohypophysis was* found affected in some way in each instance The pathology ordinarily is due to a tumor growth which destroys or causes pressure atrophy of the gland These tumors most commonly are craniopharyngiomas[19, 5, 8] Teratomas[97, 198] and cholesteatomas are relatively rare[196, 197, 198, 99] Those instances in which trauma *to the skull has been associated with the onset of the arrested growth also have* presented evidence of adenohypophysial tumors[9, 91] In some instances the pathology has consisted of extensive atrophy of the adenohypophysis presumably induced by embolism Hutchinson reported an atrophied hypophysis in a dwarf without noting any contributory factors[141, 142] Atrophy in other instances has *been caused by inflammatory processes such as tuberculosis or syphilis*[165] Tuberculous destruction of the hypophysis has been reported by Hueter[92] The writer has observed infantilistic dwarfism in an instance of Schuller Christian s disease where the xanthoma invaded the sella turcica and destroyed the hypophysis (Fig 32)

The degree of human dwarfism apparently depends on the age at which the pathological process develops and the length of time that it operates It is said that the degree of dwarfism may be related also to the extent of the damage to the adenohypophysis but there is no recorded evidence on this point Actually this may not be a reasonable assumption inasmuch as even minute remnants of *normal adenohypophysial tissue appear to be able to maintain the metabolic func*tions of the gland to a remarkable degree Possibly other endocrine or perhaps hypothalamic factors are involved in this matter as suggested by the autopsy on Berblinger s[7] dwarf referred to later on in this section

As in the case of gigantism the hypophysis was suspected of implication in dwarfism long before its growth regulating function was demonstrated Surprisingly few cases of so called hypophysial dwarfism and infantilism however have been studied thoroughly clinically and at autopsy

The first recorded instance of what has since been recognized as hypophysial

Fig 32 Schuller Christian's syndrome in a 19 year old boy Note dwarfism and genital hypoplasia with disproportionate skeletal measurements typical of eunuchoidism Autopsy disclosed complete destruction of the hypophysis cerebri Reproduced through the courtesy of the Department of Medicine Peter Bent Brigham Hospital.



dwarfism coupled with infantilism appeared in 1868 [93] Schaaffhausen's patient was a male of average intelligence, 61 years of age and 94 cm in height There were three other examples of a similar condition among his brothers and sisters The conformation of the face and cranium were childish, the testes were undescended bilaterally and the epiphyses were ununited The post mortem examination following a terminal cerebrovascular accident was incomplete but the clinical picture is almost certainly that of adenohypophysial infantilistic dwarfism In 1891 Paltauf[1 4] described a similar dwarf with infantile proportions ununited epiphyses and a markedly enlarged sella turcica In 1900 Hutchinson[14] called attention to a profound atrophy of the hypophysis in a dwarfed individual Levi's case[169] described in 1908 was a typical example of infantilistic dwarfism in which optic atrophy and x ray evidence of an hypophysial neoplasm were demonstrated The relatively frequent association of dwarfism and craniopharyngeal tumors was noted by Erdheim in 1916 [94] Several carefully studied cases of dwarfism were reported by Erdheim[198] Altmann[195] Priesel[2 5] Berblinger[1 6 9] and Cushing [8] Erdheim's case, a male of 38 142 cm in height had infantile genital organs testes, penis seminal vesicles and prostate absence of facial, pubic and axillary hair and ununited epiphyses Autopsy disclosed a benign cystic craniopharyngioma which had become calcified and partially ossified Only traces of the adenohypophysis remained In Altmann's case a female of 17 129 cm in height the epiphyses were ununited A craniopharyngioma with extreme atrophy of the adenohypophysis was found at autopsy Priesel described the case of a male 132 cm in height who showed beginning evidence of inhibited growth at the age of 15 but lived to the age of 91 His dwarfism was of the proportionate type he was of good intelligence the epiphyses all became united but his testes remained small At autopsy the neurohypophysis was found behind the optic chiasm and the infundibulum it had never come into contact with the adenohypophysis The latter was atrophic or rudimentary having been replaced almost entirely by a cyst that communicated with a widened portion of a persistent craniopharyngeal duct

Berblinger's dwarf 144 cm in height was a male who died at 22 At the age of 15 he was only 135 cm in height and grew only 9 cm between then and the time of his death He had all the physical characteristics of hypophysial dwarfism and showed signs of intracranial neoplasm including headaches vomiting attacks of vertigo diplopia left abducens paralysis and bilateral choked discs His intelligence was good X ray examination of the skull showed an enlarged sella turcica above which were some shadows due to calcification He died of pulmonary and intestinal tuberculosis and at autopsy the region of the infundibulum was found replaced by an extra sellar partly cystic craniopharyngioma The pars tuberalis of the adenohypophysis and a portion of the floor of the third

ventricle were destroyed by the neoplasm which also displaced the floor of the third ventricle upward The bulk of the adenohypophysis was flattened by pressure, and on histological examination it was found that the chromophobe cells outnumbered the chromophile cells Berblinger believed that the injury to the adenohypophysis was not sufficient to render it non functional and concluded that the dwarfism was due to interruption of the connection between the adenohypophysis and the hypothalamus, possibly by way of the pars tuberalis

Pathological Physiology

Presumably the specifically damaged elements in the adenohypophysis are the acidophile cells which secrete the hormone regulating growth A detailed account of the biochemical and physiological significance of this hormone has been recorded in Part II of this chapter In this connection it is pertinent to recall the remarkable strain of congenitally dwarfed mice, the hypophyses of which are completely lacking in acidophile cells [07, 08] This strain of black silver mouse was brought to this country by Professor L C Dunn and described by Snell [09] who found that the dwarfism is not manifest until the end of the second week of life, when the natural process of weaning normally begins Development and growth practically cease at this time and the mouse is left in an infantile condition Smith and MacDowell [07, 08] reported a complete absence of acidophiles in the adenohypophysis Unfortunately their staining technic did not reveal whether or not basophiles were present The chromophobes were found to be much reduced in number if present at all The thyroids were much below normal in weight, and their parenchymal tissue was extremely reduced in amount and separated by unusual amounts of adipose and connective tissue Some of the thyroid tissue was not organized into follicles and contained little or no colloid The vesicles which were present were lined with squamous epithelium with flattened nuclei instead of the cuboidal type ordinarily seen in normal controls The adrenal cortex was found reduced in thickness, and the characteristic zonation was absent or indistinct The medullary cells appeared to be normal and contained the usual proportion of cells showing the chromaffin reaction The gonads although markedly retarded in development did not show as profound an aplasia as might have been expected from studies of hypophysectomized rats Development of the testes and other parts of the male reproductive system appeared only to be delayed Spermatocytes were present and undergoing division in the seminiferous tubules, and in occasional tubules there were fairly numerous spermatids The testes were not of the flabby variety characteristic of hypophysectomized rats

Development of the ovary was found to be further along than that ever seen after hypophysectomy although no medium sized or large follicles or corpora

lutea were encountered The ovaries became filled with interstitial tissue Subsequent biological studies [8] disclosed that there was a greater concentration of gonad stimulating hormone in the hypophyses of the dwarfed animals than in the glands of normal, mature female mice No significant amount of growth promoting substance could be demonstrated in the hypophyses of the dwarfed mice

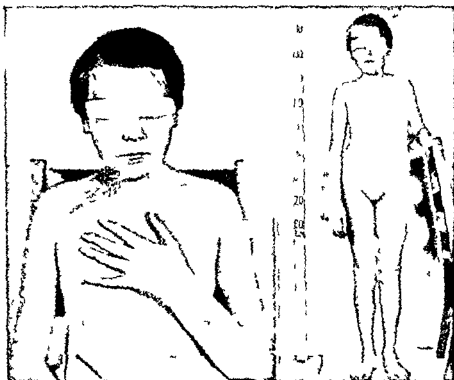


Fig 33 Hypophysial dwarfism in a 21 year old girl with chromophobe adenoma of the adenohypophysis Note childish appearance and genital hypoplasia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

Judging from the condition of the gonads one might assume that basophiles were present in the hypophysis and functioning perhaps at a reduced rate because of the absence of the synergistic influence of the acidophiles The cytophysiological significance of these studies would be greatly enhanced were the condition of the basophiles known At any rate the absence of acidophiles seems to account quite satisfactorily for the dwarfed condition of the mice and possibly for the underdeveloped state of the thyroid gland

It is tempting to consider the possibility that these congenitally dwarfed mice, whose hypophyses are lacking in acidophile cells, are akin to the primordial variety of human dwarfism Further comment on this point is superfluous in the absence of autopsy material which has been studied adequately



Fig 34 Three primordial dwarfs siblings Male aged 30 years height in shoes 43 2 inches females aged 26 and 14 years respectively heights 37 2 inches and 34 4 inches respectively After Rischbieth and Barrington

General Appearance

Hypophysial dwarfs ordinarily are of good intelligence The syndrome is characterized by a proportionate diminution in size of the trunk extremities and internal organs The hands and feet are small and delicate The infantile size and proportions of the body and limbs are retained The limbs usually are particularly short, and the proximal segment humerus or femur may be shorter than

the distal portion Owing to the shortness of the lower limbs the middle point of the body is closer to the umbilicus as in infancy instead of being at the sym physis pubis as in normal adults The features of dwarfs are fairly stereotyped The hypophysial dwarfs particularly those with infantilism have the immature



Fig 35 Primordial dwarf Mlle Anita Age 23 years height 25 inches After Rischbieth and Barrington

appearance of children (Fig 33) The head is small and the configuration and measurements of the skull are those of the child The so called sexual ateleiotic (Gilford) or primordial (von Hansemann) dwarfs whose pathology is as yet unknown also have distinctive features which differentiate them from the infan tilistic hypophysial dwarfs The face of the primordial dwarf is broad and flat the head is relatively large the bridge of the nose is undeveloped the nose is small and uptilted and the upper jaw is relatively short In typical cases although it is not universally so the facial type is so well defined that individualistic expres sion of character and personality is somewhat obliterated (Figs 34 and 35) This circumstance results in a strong resemblance between dwarfs of different families

As the childish features of the hypophysial dwarfs become lined with the super ficial markings of age the facial appearance acquires an incongruously wizened

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the eighteenth century as was Charles Stratton in the nineteenth was Joseph Boruwlaski[1, 2] His parents who were of medium size had 6 children 3 of whom males are said to have exceeded the ordinary stature while 2 sons and one daughter did not attain a 4 year old height although they reached adult age Boruwlaski matured sexually at about the age of 25 became married at 40 and subsequently begot several children

Laboratory and Roentgen Data

In addition to the general appearance and lack of sexual development the significant clinical findings in hypophysial dwarfism include a low fasting blood sugar increased sugar tolerance abnormal sensitivity to insulin a moderately decreased or normal basal metabolic rate and x ray changes in the skeleton A basal oxygen consumption of −15 to −25 per cent is not unusual Whether or not these measurements are acceptable is questionable inasmuch as adequate standards are not available for these abnormal individuals

If these metabolic results are essentially correct one could attribute them to a lack of the direct calorigenic action of the adenohypophysis in addition to a failure in the production of thyrotropic hormone with secondary hypo thyroidism The urinary excretion of neutral 17 ketosteroids and gonadotropin either is diminished markedly or absent entirely in accordance with the re ported data of Klinefelter Albright and Griswold[6] and the experience of the author

X ray examination of the skeleton shows that the long bones are small slender and fragile The development of the carpal and metacarpal centers of ossifica tions may be normal but ordinarily they are somewhat delayed and occasionally markedly behind schedule[18] [8] The epiphyses remain ununited except in those rare hypophysial dwarfs who mature sexually or in the sexually mature primor dial group of dwarfs[163] [7]

Roentgenograms of the skull of the hypophysial dwarf disclose pathognomonic evidence of adenohypophysial somatotropic insufficiency according to Mortimer Levene and Rowe Mortimer[10] and Goldzieher The face is small in relation to the cranium which thus remains largely infantile in type The brow retains the verticality of infancy The middle table of the thin and poorly differentiated calvarium is hypoplastic and can be made out only with difficulty The frontal sinuses are poorly developed and as a rule have not grown above the nasion The body of the sphenoid usually remains cancellous bone the sella turcica is infantile and the antra poorly developed The alveolar processes are hypoplastic and crowding of the teeth is marked Such crania closely parallel the results of hypophysectomy in the rat and dog[210]

expression To some extent this is due to the development of an atrophic wrinkled and pigmented skin The voice retains its childish treble pitch Dentition is very backward as a rule, to such an extent in some cases that many of the milk teeth are retained into the third and fourth decade of life The dwarfed jaws thus may become crowded with half erupted permanent teeth mingled with more or less decayed temporary teeth

Sexual Aspects

The lack of somatic development in hypophysial dwarfism is associated almost universally with retarded maturation and growth of the sexual apparatus On the other hand one may encounter instances of hypophysial deficiency, in which there is a specific lack in the production of either the growth or the gonadotropic hormones In such cases the resultant clinical syndrome is characterized by dwarfism without infantilism or gonadal hypoplasia without dwarfism respectively In patients of the latter category the skeletal measurements generally are those of the eunuchoid individual, and the total height is either "normal" or somewhat in excess of this average figure The majority of hypophysial dwarfs remain sexually infantilistic Others, who mature sexually, are encountered only relatively infrequently

The genital organs of the infantilistic dwarfs of both sexes are markedly underdeveloped In the female there is hypoplasia of the ovaries tubes, uterus, vagina and labia majora and minora The labial, pubic and axillary hair is absent *as a rule, because of the adrenocortical atrophy, which occurs secondary* to adenohypophysial deficiency In the male there is retardation in the growth and development of the penis scrotum, testes and prostate, and the testes not infrequently are bilaterally cryptorchid The growth of pubic and axillary hair is lacking as in the case of the female hypophysial dwarfs Normal growth of the external genitalia spermatozoal maturation and the development of secondary sexual characteristics occur occasionally in dwarfed individuals, who seem to show little beyond the effects of a deficiency of the growth regulating hormone The epiphyses unite at the time of sexual maturity in dwarfs of the latter type but they remain ununited indefinitely in the infantilistic group Sexual maturity occurs much more commonly in the congenital primordial variety of dwarfism than in individuals who are stunted in growth because of functional insufficiency of the adenohypophysis

Tom Thumb the famous dwarf and Charles Stratton and his equally dwarfed wife are examples of the primordial type of dwarfism Mrs Stratton gave birth to an ordinary sized female child who died of an intercurrent infection during its first year of life[173] Another dwarf of the same type, quite as celebrated in

adrenal glands which were noted at autopsy by Gilford[1 3] and by Variot and Pironneau [11]

Differential Diagnosis

Dwarfism due to adenohypophysial insufficiency must be differentiated from those cases of completely arrested or significantly inhibited somatic development, which are associated with agenesis and arrested development of the ovaries or secondary to nutritional deficiencies thyroid deficiency achondroplasia rickets and heart disease acquired congenitally or in infancy

The combined observations of a number of investigators[187 1 1 9 190 191 19] have disclosed several distinctly helpful criteria which serve to differentiate the stunted somatic growth associated with primary ovarian deficiency from dwarfism due to adenohypophysial pathology In general patients with primary ovarian insufficiency are relatively short rather than dwarfed in stature, and they appear to be well developed and nourished rather than frail and underweight as is the case in hypophysial dwarfism Both conditions are characterized by sexual infantilism with complete absence of the so called secondary sex characteristics but there is a limited to moderate growth of axillary and pubic hair in the syndrome of ovarian deficiency, whereas none at all grows in the hypophysial dwarf The latter has been attributed to atrophy of the adrenal cortex secondary to adenohypophysial deficiency[18 190 19] The bone age of hypophysial dwarfs may be considerably retarded while that of patients with primary ovarian insufficiency is retarded only slightly if at all Certain laboratory studies have been especially useful in this differential diagnosis The hypophysial dwarfs show increased sugar tolerance marked sensitivity to insulin and markedly diminished or absent excretion of urinary gonadotropin and neutral 17 ketosteroids In the case of primary ovarian insufficiency there is no significant deviation from the normal average response to the administration of glucose or insulin the urinary content of FSH is markedly elevated as a rule and the 17 ketosteroid excretion is only slightly decreased The excretion of urinary gonadotropin is not elevated invariably to a marked degree in patients with primary ovarian deficiency The reason for this unexpected discrepancy is not apparent unless one assumes that the gonadotropic activity of the adenohypophysis is damaged selectively coincidentally with the agenesis or arrested development of the ovaries in such cases

The differentiation of hypophysial dwarfism from hypothyroid nanosomia is a relatively simple matter even though a number of important abnormalities of development are common to both of them The essential characteristics of the hypothyroid dwarf vary with the age of the patient as one might expect from a disorder which cripples the various integrated phases of somatic sexual and mental development For the present purpose it is sufficient to point out that before the

Clinical Course

The growth behavior of hypophysial dwarfs lacks uniformity The disorder may appear at any age beginning shortly after birth Many of the dwarfs cease to grow entirely in childhood or youth some continue to grow at a slow pace into the third or fourth decades as long as the epiphyses remain ununited while occasionally growth ceases only for a time after which it is renewed to a limited extent The latter also may be characteristic of the primordial dwarfs and occurred in the case of the celebrated Jeffrey Hudson, who remained 18 inches tall from 8 to 30 years of age, after which he grew to 3 feet, 9 inches[1 3]

The hypophysial dwarf in contrast to the giant has a relatively long life expectancy unless there is excessive enlargement or malignancy of the hypophysial tumor or unless progeria develops Since most of these tumors are benign, they are not actively detrimental to life

Hypophysial dwarfism has been noted in association with adiposogenital dystrophy and diabetes insipidus[1] , ordinarily, however, these dwarfs are not obese

Progeria —Progeria is a rare complication of hypophysial dwarfism which develops at a relatively early age and is progressive It is characterized clinically by cachexia premature senility and infantilistic dwarfism Hutchinson s patient[1 3] who showed signs of this condition at 3½ years of age died at 14 The skin is thin, dry and old looking Axillary pubic and facial hair are absent, a sparse growth of hair may be present on the scalp eyebrows and eyelids The extraordinary emaciation reveals even the nasal cartilages The muscles are poorly developed and weak Gilford s patient[173] who died at 18, had ununited anterior fontanelles at 14 years of age when he was last studied His dentition was delayed and crowded his voice was pitched high and his sexual development seriously impaired He died a cardiac death At autopsy there was extreme emaciation a persistent enlarged and fibrous thymus and extensive atheroma of the mitral and aortic valves the coronaries were solid thick cords and completely blocked the kidneys were fibrous senile the suprarenal capsules were shrivelled, the stomach and intestines were extremely atrophied the liver relatively large, the long bones small and delicately formed with ossification generally a little premature The brain was said to be normal and examination of the hypophysis was passed over casually because it seemed unimportant A third case has been reported by Variot and Pironneau [11]

Progeria appears to be the juvenile form of Simmonds cachexia in combination with hypophysial dwarfism but positive proof of this clinical impression is not yet available This assumption would account adequately for the atrophic

spread belief these developmental anomalies are by no means pathognomonic of juvenile myxedema nor can they be used to differentiate this condition from hypophysial dwarfism The extent of the delay in these processes of bone development and growth usually is less in hypophysial dwarfism than in hypothyroidism but the fact that the difference is quantitative not qualitative obviates its usefulness as a differential diagnostic point As a matter of fact there are individual examples of hypophysial dwarfs in whom these defects are as striking as in the nanosomia of hypothyroid origin

In infantile myxedema the circumference of the skull does not correspond to the age of the individual but is distinctly larger in proportion to the rest of the skeleton This is true also of another type of dwarfism viz that described by von Hansemann as primordial nanosomia and by Gilford as sexual ateleiosis It is this writer s impression however that the infantilistic dwarf of Paltauf s type which is identical with asexual ateleiosis of Gilford von Hansemann s infantile dwarf whether of hypophysial origin or secondary to nutritional deficiencies etc is more likely to have a skull relatively small for his age but which is in proportion to the size of the rest of the skeleton

So far as the bones are concerned the only differential point between hypophysial and hypothyroid dwarfism lies in the x ray appearance of the shaft of the long bones In the former the bones are slender and fragile in appearance and the cortex is thin in the latter the bones are relatively heavy and thick and show a slight degree of sclerosis Breus and Kolisko and Bircher[2 3] have observed an additional differential point between endemic cretinism and the Paltauf type of dwarfism viz that the endemic cretin has a disproportioned skeleton because epiphyseal union takes place at a different rate and to a different degree in various bones whereas all epiphyseal closures are delayed equally in hypophysial dwarfism

The hematopoietic system suffers seriously in hypothyroidism the hemoglobin is reduced relatively more than the erythrocytes In hypophysial dwarfism the total erythrocyte count ordinarily is within normal limits but the hemoglobin may be somewhat reduced In both conditions there is a well marked relative lymphocytosis and eosinophilia

The rachitic and achondroplasic dwarfs offer no problem in differential diagnosis X ray studies of the ends of the long bones and the classical bony deformities of the rachitic individual i e skull changes pigeon breast Harrison s groove rosary bow legs etc leave little doubt as to the etiology of this type of somatic maldevelopment The achondroplasic dwarf is recognized readily by the disproportionate growth of trunk and extremities Such persons have a full sized head and trunk associated with incongruously short extremities Not only are the long bones of the arms and legs abbreviated but the base of the cranium is dis-

fourth and fifth year the hypothyroid dwarfs do not exhibit the coarse, dry, thick integument usually associated with juvenile myxedema. Although the skin of the infant hypothyroid is thicker than normal, it remains quite smooth, and there are subcutaneous fatty pads at the nape of the neck and in the supraclavicular regions. These fatty pads are absent, and the skin is thin and soft in the hypophysial variety of dwarfism. The face of the hypothyroid individual derives its characteristic cretinoid appearance from the position of the horizontally placed, slit like eyes and from the depression at the root of the nose, which is due to a delay in development of the nuclei of ossification of the vomer. In addition there is a vacuous facial expression and behavioral evidence of retarded mental development. The hypophysial dwarf, on the other hand, retains a childish facial expression and may be retarded psychologically but not mentally. Di Gaspero [1] attaches a special significance to the retention of childish ideas of values and logic. He finds in the infantilistic dwarf a childish instinct for mimicry and a certain attitude of anxiety and non independence. Anton [13, 14], who is in general accord with Di Gaspero, has observed also that these individuals usually lack the childish tendency toward gaiety and freedom.

In both of these types of dwarfism there is delayed and abnormal dentition. The milk teeth develop very slowly and finally remain partially retained. Rudiments of the permanent teeth become mixed with the milk teeth. Failure to walk and talk at the usual age, the enlarged thick protruding tongue, the hoarse cry, the umbilical hernia, the protuberant pot belly and chronic constipation are additional clinical features limited to juvenile myxedema. A serious retardation in genital development is common to both forms of dwarfism. In the female there is marked hypoplasia of the external and internal genital organs. The labia majora are stunted and do not cover the labia minora, the uterus is underdeveloped, and the breasts fail to grow. In the male the penis is small, and the testicles do not descend ordinarily. If they do enter the scrotum, they usually remain infantile. There is no change in voice unless sexual maturity takes place. Pubic and axillary hair ordinarily is absent in both sexes.

In general the dwarfed skeleton retains the child like body proportions in both disorders, and a delay in closure of the fontanelles also is characteristic of both conditions. Argutinsky [15] has observed that there is a greater delay in the development of the bone nuclei than in the linear growth of the long bones in sporadic cretinism. Thus, if the height of a 20 year old cretin corresponds to that of a 6 year old normal child, the appearance of the nuclei of ossification are even considerably further behind. Delay in the closure of epiphyses and retardation in the time of appearance and development of the various centers of ossification are constant features of hypothyroid dwarfism[1, 13, 15, 16, 17, 18, 19, 20, 21], which can be determined conveniently by x ray examination of the wrist. Contrary to wide

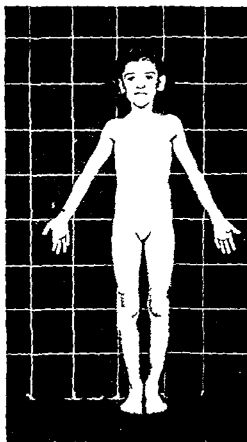


FIG 36 Infantilism and dwarfism History of severe qualitative and quantitative nutritional deficiencies Marked and immediate growth response to balanced diet supplementary vitamins and methyl testosterone Age 9½ years Reproduced through the courtesy of E Kost Shelton MD

" hypophysial dwarfs 3 of whom eventually turned out not to be of hypophysial origin [5] Another factor contributing to the difficulty of evaluating the efficacy of therapy or lack thereof is the inadequately controlled experimental conditions under which the therapeutic trials are made Many of the cases treated successfully are given physiological doses of thyroid simultaneously with an adenohypophysial growth promoting extract without first testing the patient s growth re

proportionately short so that the face is flattened and depressed at the nasion saddle shaped, and the forehead consequently is prominently rounded The epiphyseal cartilages in the extremities and the basicranial cartilage in the head are deficient with more or less connective tissue hyperplasia and fail to give the usual growth of the long bones In some of these dwarfs the coccygeal vertebrae are fused and bent in direction The extremities are short and considerably bowed and twisted As a rule the proximal segment of both extremities, humerus and femur, are more shortened than the distal segments The hands and feet may be simply stocky and wide in appearance The posture of the hands and feet tends to abduct or outspread the digits to varying degrees The arms and hands are moved in a characteristic manner The hand cannot be brought to the mouth without abducting and raising the elbow almost shoulder high This condition is caused by the spiral twist in the long bones, which affects the plane of flexion of the elbow joint The sexual development of the achondroplasic dwarf generally is quite normal and the epiphyses unite at the proper time Occasional instances of a slightly delayed closure of the epiphyses are encountered in individuals with a somewhat retarded sexual development

The obvious importance of nutritional factors to the normal progress of growth (Fig 36) makes it essential to investigate the patient s past history thoroughly for evidence of malnutrition either as the result of socio economic and environmental conditions or of gastrointestinal renal or cardiac disturbances The distinction between primary and hypophysial dwarfism or infantilism and retarded somatic and sexual development secondary to nutritional disorders is not a simple one to make In many instances the two groups of conditions overlap, especially when malnutrition has damaged the adenohypophysis secondarily The attempt at differential diagnosis is important however because of the necessity for specific therapy, viz a well balanced diet, supplementary vitamins, sunshine, etc

Treatment

There is every reason to believe that the adenohypophysial growth hormone has been used more widely in the treatment of hypophysial and other forms of dwarfism than the relatively few reports in the literature would indicate This probably signifies that many of the studies yielded negative results which investigators were loth to report Furthermore the results of the published investigations are variable and contradictory These inconsistencies may be attributed in part to certain difficulties in the diagnosis of hypophysial dwarfism Even in the hands of experienced investigators the nature of the fundamental disorder frequently is not established until the clinical course of the patient discloses it Such was the report of Shelton Cavanaugh and Evans[2 4], who studied a series of 6

under chorionic gonadotropin therapy an increase in the growth rate beyond the expected average has been observed by Lurie and Hertzman[1] Dorff[35] Thompson and Heckel[8] and Finkler, Furst and Cohn The range of dosage used to accomplish these results has been fairly wide averaging from a total of 9 000 to 40 000 rat units which are equivalent to international units Treatment usually has been administered in doses of 250 to 500 i u per week over a period of 4 to 8 weeks with intervals of 4 to 6 weeks between each series of injections

As in the case of chorionic gonadotropin various compounds of testosterone have been administered to somatically and sexually underdeveloped boys principally for the treatment of their gonadal and genital hypoplasia Various recognizable endocrinopathies characterized by these deficiencies have been treated successfully with testosterone[6, 11, 3] Most investigators have resorted to a descriptive terminology rather than one aimed at stating the primary nature of the growth disorder For instance Finkler Furst and Cohn include many instances of cryptorchidism and growth retardation among their patients but without any attempt at further diagnosis It is this writer s experience that testosterone propionate or methyl testosterone are effective in the treatment of hypophysial dwarfism associated with sexual infantilism[8]

There is good experimental evidence which relates the efficacy of testosterone to growth Castration of male rats in early life results in significant inhibition of general somatic development and retardation in body length as compared to normal controls Rubenstein and Solomon[9] have reported an increase in the body length of white rats following the administration of small doses of various testosterone esters whereas large doses exert a depressing effect which exceeds that of castration alone Turner and associates[41] also found that large doses of testosterone propionate given over prolonged periods of time did not accelerate body growth or skeletal maturation in rats except in isolated instances

A good deal of controversy has centered about the possible deleterious effects of testosterone therapy viz the hazards of testicular damage, premature closure of the epiphyses and macrogenitalia Until relatively recently it was believed because of limited physiological experiments that the administration of testosterone always induced atrophy of the testes although it stimulated the growth of the penis scrotum seminal vesicles and prostate as well as development of pubic and axillary hair Rubenstein and Kurland[4] state however that small doses of testosterone propionate (5γ) injected daily into male rats from 22 to 32 days of age results in a significant increase in the weight of the testes and stimulation of proliferation of the germinal epithelium but maturation of the spermatozoa remained unaffected With much higher doses (50γ) the testicular weight diminished but all testes showed signs of increased germinal proliferation Intermediate doses affected the testes adversely in every respect Shay and asso

sponse to thyroid alone [6] Although the thyroid hormone may enhance the growth promoting qualities of an adenohypophysial extract and from this point of view seem indicated there is no way of knowing what thyroid alone might have done Even when adequate clinical controls are set up, an untreated hypophysial dwarf suddenly starts growing to the extent of 6 inches (15 2 cm) in 22 months It is doubtful moreover, whether the earliest reported successes can be accepted as such, because of the relatively low growth promoting potency of the extracts then in use

A survey of the literature and the writer s own experience with the therapeutic efficacy of adenohypophysial growth promoting extracts in hypophysial dwarfism indicate that isolated cases seem to have responded significantly but the results in general leave much to be desired The latter is decidedly not applicable to *the growth stimulating effects which have been observed after the use of chorionic* gonadotropin or testosterone propionate or a combination of the two

The value of chorionic gonadotropin as a therapeutic agent in dwarfism was recognized as a result of its use for the correction of genital and gonadal hypo plasia Following the discovery of this gonad stimulating substance in pregnancy urine by Aschheim and Zondek [27], Engle demonstrated [8] that an increase in the rate of growth of the sex organs of the immature rat could be produced by its *injection* Schapiro [9] *subsequently applied this knowledge clinically* to cases of genital hypoplasia and cryptorchidism The use of chorionic gonadotropin be came more extensive following Engle s demonstration [1] that testicular descent was induced in monkeys with delayed puberty by injecting extracts of pregnancy urine

Since then there has been accumulated an extensive literature dealing with this type of endocrine therapy for cryptorchidism This has been reviewed by Bigler Hardy and Scott [31] Nixon and Finkler, Furst and Cohn [9] among others Unfortunately in most of the reported cases the clinical emphasis has been on the condition of the genitalia and little or no attempt was made to differentiate one type of growth retardation from another The treated patients showed almost invariably a combination of various degrees of dwarfism genital hypoplasia and gonadal underdevelopment including cryptorchidism So far as one can judge instances of hypophysial dwarfism are to be found among these successfully treated examples of sexual and somatic infantilism

A wide divergence of opinion is to be found among investigators concerning the efficacy of this form of therapy for cryptorchidism Reports of successful re sults range from 20 to 70 per cent More extensive experience in the selection of patients has disclosed that true cryptorchidism has yielded to this form of therapy in an average of about 30 to 40 per cent of the cases [1 3 33 234]

Coincident with the improvement in the genital development of these boys

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ciates [43] found similarly that large doses resulted in an increase of testis weight and stimulation of spermatogenesis They concluded that the immature germinal epithelium can be stimulated to increased activity but not to earlier maturation It is still too early to discuss this problem as it applies to human beings with any degree of assurance but in this writer s experience no harm has been done with moderate dosage [3] It is certainly clear that moderate amounts of the testosterone esters do not produce untoward epiphyseal development or premature closure of the epiphyses[16 34 44 4 40 4 48]

Ordinarily a favorable response in linear growth and sexual development is elicited following the administration of 10 mgm testosterone propionate parenterally 3 times a week or 10 to 20 mgm methyl testosterone orally 4 to 7 times per week The dose has to be adjusted in each case so that neither frequent priapism nor too rapid growth of the penis occurs

Dwarfism also is discussed by Arthur Grollman in Vol III, Chapter XIX, of Oxford Medicine

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Cytology with Special Reference to Pituicytes

As compared with the adenohypophysis relatively little is known of the cytology of the neurohypophysis. Data available at present indicate that there are several different varieties of cells in the lobus nervosus, a subdivision of the neurohypophysis which has been studied more particularly than the infundibular stem or the median eminence of the tuber cinereum. The cells which have been described *include the neuroglia like pituicytes, isolated nests of large pale cells* and invading basophile cells which take origin from the pars intermedia. Undoubtedly there are other parenchymal cells which remain to be recognized and described, judging from the complex cytological appearance of this portion of the gland. In this connection it is well to recall that apparent cytological differences *between cells of the same general type may represent various metabolic phases of cellular activity rather than functionally different parenchymal cells*. An excellent example of this general rule was encountered by Gersh in the pituicytes of the rat's neurohypophysis which changed remarkably with hydration and dehydration of the animal.

The pituicytes, so named by Bucy, are to be found in all divisions of the neurohypophysis. *The topographical distribution of these cells is coextensive* with the sites from which the antidiuretic principle has been extracted. Moreover the pituicytes have been identified in all orders of mammalia whose glands have yielded this hormone. It is interesting, furthermore, that the distribution of these cells is that which might be expected from the most recent conception of the pathogenesis of diabetes insipidus. In appearance the pituicytes are fusiform *and irregularly shaped cells provided with delicate branching processes*. Geiling and Robbins[22] report that in the white whale these cells have stout processes which end with expansions on the connective tissue of the capsule or of the walls of the abundant blood vessels. Geiling[1] likens their structure to ependymal spongioblasts of the embryonic central nervous system or to the cells of ependymal tumors.

Some of the pituicytes are definitely granular, while others are devoid of granules, probably depending on the phase of their functional activity. Although superficially similar to the neuroglia of the central nervous system they are distinctive cytologically from these and all other cells of the hypophysis cerebri. In the various orders of mammalia studied by Gersh[19] there is clear-cut differentiation of pituicytes from other cells of the hypothalamo hypophysial area. In the neurohypophysis *of the rat and mouse these parenchymatous cells contain cytoplasmic inclusions rich in neutral unsaturated fats which are stained by Sudan III* and reduce osmic acid readily. In ox glands the histochemical reactions of the intracellular inclusions indicate that they are protein in nature. The cytoplasmic

PART V

CYTOPHYSIOLOGY, BIOCHEMISTRY AND PHARMACOLOGY OF THE NEUROHYPOPHYSIS

HISTOLOGY AND CYTOLOGY OF THE NEUROHYPOPHYSIS

General Histological Characteristics

It was indicated in the opening paragraphs of Part I that the neurohypophysis consists of a functional unit which is made up of the median eminence of the tuber cinereum, the infundibular bulb the infundibular stem and the infundibular process In general these neural subdivisions of the hypophysis cerebri contain the following histological elements (a) a meshwork of connective tissue fibrils, which are composed largely of reticulin with some collagen according to Bucy[1] (b) a capillary plexus the origin and distribution of which has been described under an appropriate heading elsewhere in this chapter (c) unmyelinated nerve fibers which enter the neurohypophysis via the median eminence and infundibular stem in the form of the supraoptico hypophysial the paraventriculo hypophysial and the tubero hypophysial tracts These tracts give off innervating fibers to the various parts of the neurohypophysis through which they course, and finally spread out into a dense meshwork in the infundibular process Here they come into pericellular relations with the pituicytes which will be described later It has been established with some certainty that the paraventricular nucleus sends only a few fibers into the processus infundibuli and that most of its fibers end in the region of the supraoptic nucleus and the median eminence of the tuber cinereum[2] The supraoptic nucleus is thought to be the origin of nearly all of the fibers entering the processus infundibuli and the so called tubero hypophysial tract may arise from the attenuated posterior end of the supraoptic nucleus according to Rasmussen[3] (d) relatively few unmyelinated nerves which are the post ganglionic fibers of the superior cervical sympathetic ganglia and enter the neurohypophysis with its vascular supply (e) various types of cells including the specialized glial cells known as pituicytes large pale cells of unknown origin and function[4, 6, 8], basophile cells which arise from the pars intermedia and invade the processus infundibuli wandering cells[7] and mast cells[9]

connected with the hypophysial cleft by ducts through which a seroalbuminous secretion is poured into the cleft Bucy believes there can be little doubt from the histological appearance that they are true glands In accord with Erdheim[14] and Lewis and Lee[17] Bucy regards them as derivatives of the buccal mucosa and thus relates them to the salivary glands Histogenetic studies indicate that they *belong to the pars intermedia* Macroscopically the glands *are composed of numerous branching acini uniting at a common duct They are lined by a single* layer of pyramidal cells with a pale spherical nucleus near the base The apices of the cells contain a highly refractile colloid like substance whereas the cytoplasm is finely granular in general The duct of the gland is formed by a low cuboidal epithelium quite unlike that of the acini

Beyond four years of age the number of these glands decreases and certain of them become distended with their own secretions forming small colloid cysts which are encountered near the junction of the adenohypophysial and neurohypophysial *tissues in the zone of the* pars intermedia These cysts are lined by a *flattened cuboidal epithelium among the cells of which a few basophilic cells can* be seen frequently The basophiles are relatively large with a round or ovoid shape and their cytoplasm is filled with many basophilic granules In adults masses of basophilic cells appear in the lobus nervosus[7, 8, 18, 19] in addition to colloid cysts Apparently the basophilic cells develop at least in part from the glandular structures

Guizzetti[4, 15] has observed narrow cords of cells arising from the pars intermedia and extending into the pars nervosa in the first year of life About the seventh year *these* cells become transformed into basophiles This invasion and *transformation is not a constant finding* Guizzetti observed it *in one third of* the cases between 10 and 20 years *two thirds between* 20 and 30 *and four fifths* between 30 and 85 years Sparks Rasmussen[19] and others before them have called attention to the fact that the basophilic cell invasion is greater in the hypophyses of males than of females Careful statistical studies have failed to correlate the extent of invasion with various clinical disorders characterized by hypertension[7, 8 ... 3] The most extensive invasion is said to take place from that part of the pars intermedia which is in contact with the inferior portion of the lobus nervosus[14, 15] Where the basophilic invasion is limited to one area it is also more likely to extend into this part of the neurohypophysis

The Hyaline Bodies of Herring

Herring was among the earliest to call attention to the loose mesh like appearance of the tissue of the neurohypophysis He observed that interstitial spaces lined with endothelium in some instances contained peculiar homogenous

granules are very nearly uniform in size in any particular cell but may vary considerably in different cells according to Gersh[10] Serial sections of the pituicytes disclose that the granules extend far out into the cell processes These are the cells undoubtedly in which Bucy[1] observed granules of brown pigment, which stained readily with neutral red The amount of the pigment appears to increase gradually with age [8] Kraus has made similar observations, but since the hypophyses from elderly individuals occasionally show little or no pigment, he believes that there is no significant relation between age and this type of pigment Presumably this pigment is identical with the cytoplasmic inclusions which have been described by Gersh[10]

The isolated nests of large pale cells, which occur in the processus infundibuli, probably are of physiological significance but the latter has not been determined as yet They have been described by Kraus, who quotes several authors concerning them by Simonds[4] who describes them in two cases, by Sparks, who pictured them in one case by Sternberg and Priesel[6], who found that they measured 30 to 50 micra in diameter and by Parsons[3], who observed them in 13 of 107 glands which he studied

These nests of cells vary in size from those containing only a few cells to groups of cells which measure 0 5 mm in diameter The nests usually are single, and Parsons states that ordinarily they are found to one side of the median line in the posterior half of the lobus nervosus These cells have a distinct cell boundary, which stains more intensely with aniline blue than other parts of the cell The cytoplasm is abundant and loosely packed with granules which take the acid dye when stained with hematoxylin and eosin The nucleus is large and vesicular and is located eccentrically The nests lie in the interstices of the tissues of the lobus nervosus

Small capillaries and light strands of connective tissue penetrate between these cells whose function and origin still remain to be determined Kraus[5] has suggested that they represent cell nests of ependymal origin They may be derived from the saccus vasculosus to which reference was made in Part I of this chapter Parsons has observed single cells similar to but smaller than those just described which occur in the interstices of the lobus nervosus They have a normal nucleus and a distinct cell membrane which distinguishes them from the structures that Cushing[1] [13] thought were derived from the basophilic cells in the lobus nervosus

Numerous careful observations which have been made of the epithelial cells in the lobus nervosus indicate that their cytological characteristics and distribution change with advancing age but the physiological significance of these alterations is wholly obscure Tubulo racemose glands are a feature of the neurohypophysis during the first four years of life according to Guizzetti[14] [15] They are

Pharmacology and Methods of Assay of the Neurohypophysial Principles

General Considerations

Only three of the numerous biological activities which have been attributed to neurohypophysial extracts are sufficiently well characterized to merit identification as pharmacological properties of the neurohypophysis itself These are the effect upon mammalian blood pressure upon uterine muscle and upon the rate of excretion of urine viz the pressor oxytocic and antidiuretic activities respectively

Other effects that have been observed may be due to substances which arise in portions of the hypophysis other than the lobus nervosus or they may have been elicited by substances like histamine which are extractable from a variety of animal tissues

The Pressor Effect

The bioassay method for the pressor principle has been developed largely through the studies of Hamilton and Rowe [32] [33]

The solution to be assayed is injected into the leg vein of an anesthetized cat or dog and it is followed by an injection of the reference standard after an interval of 15 minutes The pressor standard used is a powdered preparation of the desiccated lobus nervosus of fresh beef glands which contains 2 International Pressor Units per mgm when prepared as prescribed by the U S Pharmacopoeia This preparation has been adopted as the standard for pressor and antidiuretic assay [6] and it has been agreed further that 1 mgm of the standard powder contains 2 units of each of the three pharmacological activities of the neurohypophysis

The pressor assay dose varies between 0 1 and 0 5 units 0 05 to 0 25 mgm of the standard powder This dose usually induces an increase in blood pressure of about 10 mm of mercury The mercury manometer which registers these changes in blood pressure in a cannulated carotid artery transmits the impulse to the smoked drum of a kymograph Alternate injections of the unknown and the standard are made at 15 minute intervals until the increase in blood pressure due to varying amounts of the unknown is approximately equal to that produced by the standard in at least two successive paired experiments

Since the pressor content of the standard dose is known the ratio between the heights of the standard and unknown responses gives the pressor content of the unknown substance which has been injected The accuracy of this method is said to be ± 20 per cent

or granular clumps of material, which varied considerably with respect to size and shape These tissue spaces occurred between parenchymal cells, which are now known as pituicytes and extended throughout the neurohypophysis, including its infundibular stem and medium eminence Herring postulated that these hyaline bodies were the product of secretion of the pars intermedia, and that they ascended the infundibular stem to enter the cerebrospinal fluid through the wall of the third ventricle

Many investigators have been concerned with the origin, physiological significance and fate of the hyaline bodies since Herring s report Most authors have referred to them as colloid and thought that they represented the product of secretion of one or another of the various parts of the hypophysis cerebri Tello [3] and Bucy on the other hand regard the Herring bodies as degenerated end bulbs of the nerve fibers of the hypothalamo hypophysial tracts, which terminate among the pituicytes The most recent attempt to interpret the significance of the Herring bodies is that of Gersh [4], who came to the conclusion that they are histological artifacts which do not exist in the living animal His studies indicated that this material had the solubility properties of an albumen and occurred as a protein which was uniformly distributed in the intercellular tissue fluid of the neurohypophysis He postulated furthermore, that this substance represented plasma proteins, which had passed through the capillary wall because of its great permeability to particles of colloidal dimensions " On the basis of studies which were mentioned without details Gersh concluded that there was no identity between this uniformly distributed protein and the pressor principle One might raise a question concerning the propriety of using the term artifact, to characterize the Herring bodies It implies that they do not exist except as an accident of technic The fact that these so called bodies are altered in size, shape and distribution with variations in the rapidity of fixation should not affect their significance in the physiological scheme of things Evidence cited further on in this section indicates that the neurohypophysial principles are polypeptides with molecular weights between 600 and 2 000 [6 7 9 0 30] There is reason to believe, furthermore that a homogenous protein possessing the pharmacological activities of all three of the neurohypophysial hormones has been isolated from the lobus nervosus of oxen[31] and ultracentrifugal data support this evidence In view of these chemical and physical properties it seems desirable to reinvestigate the abundant protein material of the Herring bodies with the thought that they may represent histochemical evidence of the hormonal secretion of the pituicytes In this connection one might point out that the extent of distribution of this protein material is identical with that of the pituicytes which may be a more likely reason for its presence in the region of the tuber cinereum than the reason advanced by Herring[2]

several rats in doses of 5 c c per 100 gm body weight The solution to be assayed is injected subcutaneously into each animal and the rats are caged together The time is determined for the rate of urine excretion to reach a maximum or for the urine excretion to equal 50 per cent of the administered water This experiment is controlled by an equal number of rats treated similarly except that a known amount of a solution of the standard powder is injected instead of the unknown solution The dose of standard powder used for assay is approximately 0 006 units per 100 gm body weight Usually this amount reduces the rate of urine excretion to about 50 per cent of that found in the untreated hydrated animal The ratio between the standard and unknown time intervals serves as a basis for calculating the antidiuretic activity of the unknown This bioassay method is capable of differentiating doses differing by as little as 0 002 unit which is equivalent to about one microgram of standard powder The experimental error is in the vicinity of ± 20 per cent if the test animals are selected properly

Biochemistry of the Neurohypophysial Principles

Evidence Bearing on the Unitary and Multiple Concepts of Molecular Configuration

It is not known definitely whether one or more than one active principle exists in the lobus nervosus under physiological conditions Abel and his co workers[41] have suggested that the oxytocic antidiuretic and pressor activities were properties of a large labile mother molecule Evidence for this assumption was offered recently by Van Dyke Chow Greep and Rothen[3] who isolated from the lobus nervosus of oxen a protein which appears to be homogenous and which possesses pressor oxytocic and antidiuretic activities Furthermore studies with the ultracentrifuge have disclosed that the pressor and oxytocic activities in the pressed juice from fresh glands may be associated with a rapidly sedimenting substance presumably a protein which is not present in purified preparations of the two principles

Chemical and Physical Characteristics of the Pharmacologically Active Principles

None of the three neurohypophysial principles which have been enumerated has been prepared in pure crystalline form Fractionation procedures have yielded non crystalline amorphous preparations either of high pressor potency and very low oxytocic activity or high oxytocic potency and negligible pressor activity There is considerable additional evidence which indicates that the pressor and

The Oxytocic Effect

The official method of the U S Pharmacopoeia XII is a sensitive modification of the original uterine strip procedure[37 38] This method makes use of healthy, virgin, non estrous guinea pigs weighing between 175 gm and 350 gm It is recommended that the young female guinea pigs be segregated at the time of weaning and kept thereafter out of the sight and smell of males

The guinea pig is prepared for experimentation by a blow on the head or by decapitation and the entire uterus is removed *from the body immediately One* horn of the uterus is suspended in a chamber containing oxygenated Locke Ringer s solution at a constant temperature of 37° C One end of the horn is fixed and the other, or free end is attached to a light muscle lever which registers the extent of movement on a kymograph drum The lever may be weighted, if *necessary but the amount of this weight must not be changed* while the contractions constituting the assay are being obtained When the uterus is completely relaxed which generally takes about 15 to 30 minutes, the assay may be started Suitable quantities of the standard solution and of the preparation to be assayed are diluted with an isotonic solution of sodium chloride The solution to be assayed and the standard solution, containing 2 oxytocic units per mgm of standard powder, are added to the bath alternately in varying doses until quantities of the two solutions are found which give equal submaximal contractions in at least *two successive pairs of responses, i e a series of four contractions of* approximately the same height The bath solution is discarded and replenished after each contraction A third dose of the standard solution, which is 25 per cent larger than the two preceding doses of the diluted standard solution then is administered The first four contractions constitute an assay, if the difference in height between the highest and lowest of these four is less than half the difference in height between the lowest of the four and the contraction resulting from the reference standard the dosage of which was increased by 25 per cent The oxytocic activity *of the preparation to be assayed is calculated in terms of* U S P Posterior Pituitary Units from the ratio between the unknown and standard responses

Owing to the many variable factors in the assay of the oxytocic principle, an accuracy of ± 20 per cent is acceptable

The Antidiuretic Effect

The bioassay method usually employed for the *quantitative determination of* the antidiuretic hormone is the Burn[39] modification of the Gibbs[40] technic Water is administered by stomach tube or intraperitoneal injection to each of

observations because a well defined connective tissue septum makes possible a complete separation of the lobus nervosus (infundibular process) from the ad joining lobus glandularis Furthermore there is no histological evidence of a pars intermedia in the chicken or the whale[1] It was possible thus to prepare extracts of the adenohypophysis and neurohypophysis free of each other and un contaminated with pars intermedia Such extracts of the infundibular process contain a concentration of antidiuretic hormone which equals that extractable from the lobus nervosus of the ox gland[11] and this hormone is not to be found on assay of the adenohypophysial extract[1] These conclusions have been confirmed by histological and pharmacological studies in cats with experimental diabetes insipidus The infundibular process which is atrophic in such cats contains greatly reduced amounts of antidiuretic principle as compared with normal ani mals while the pars tuberalis and pars intermedia of the adenohypophysis were found to be anatomically and pharmacologically normal in operated animals with chronic polyuria[9] It appears to be functionally significant furthermore that the pattern and permeabilities of the vascular bed of those portions of the neuro-hypophysis in which the antidiuretic substance is elaborated have special char acteristics which differ from those observed in other parts of the hypophysis and central nervous system The vascular pattern of the infundibular process extends over the infundibular stem into the median eminence where it is sharply de marcated from that of the hypothalamic circulatory system and the permeabili ties of these capillaries differ from those of all other vessels in the other portions of the hypophysis and the remainder of the tuber cinereum[60, 15]

Secretion of the Antidiuretic Substance by the Pituicytes

Functional Innervation of the Pituicytes — The secretory cells of the median eminence of the tuber cinereum are connected with the paraventricular and supra optic nuclei of the anterior hypothalamus by well defined neural pathways the paraventriculo hypophysial and supraoptico hypophysial tracts Another group of fibers constituting the tubero hypophysial tract is thought by some[53] to take origin in the nuclei of the tuber cinereum but Rasmussen states that it may arise from the attenuated posterior end of the supraoptic nucleus These nuclei of the hypothalamus the neurohypophysis and the fiber tracts which connect them, represent a functional unit Pathological destruction or ablation of the neurohy pophysis results in atrophy of the cells of the hypothalamic nuclei and similar damage to the supraoptic nuclei is followed by atrophy of the neurohypophysis Transection or destruction of the supraoptico hypophysial tract results in cellular degeneration of the lobus nervosus and the hypothalamic nuclei and diabetes insipidus occurs if the lesions are bilateral It has been demonstrated that per

oxytocic activities of the neurohypophysis can be separated quantitatively[4 43 44 4 46] One is justified therefore, in referring to these substances as hormones Although Van Dyke[4] believes in the chemical identity of the pressor and antidiuretic principles, others differ from this viewpoint Kamm and associates[4] found that there was extremely little antidiuretic activity in purified oxytocic fractions but large amounts in potent pressor preparations Furthermore, Gilman and Goodman[41] observed that antidiuretic activity is resistant to the action *of certain reducing agents which destroy oxytocic activity* These studies indicate that the oxytocic principle probably is not concerned with antidiuretic activity The relation of antidiuretic to pressor activity has been investigated by Heller[48] who noted that pressor activity was lost slightly more rapidly than antidiuretic activity during heat inactivation over a pH range of 0 57 to 10 0 This suggests that these two pharmacological effects likewise are due to separate principles

Studies by du Vigneaud and associates Irving and du Vigneaud[7], Potts and *Gallagher*[30] *Stehle and Trister*[6] *and Stehle and Fraser*[9] *have disclosed that* molecules responsible for pressor and oxytocic activities contain amino acids joined in peptide linkage and that the presence of the intact peptide structure is essential for the pharmacological activity of these molecules These two active principles appear to be polypeptides with molecular weights between 600 and 2 000 [9 30 32] They probably contain cystine tyrosine and arginine and possibly also proline and leucine or isoleucine These five amino acids account for only about 35 per cent of the molecules assuming that only one molecule of each amino acid is present *Judging from this evidence there are no striking chemical or* physical differences between the two principles Cohn Irving and du Vigneaud[46] have demonstrated that the pressor principle is definitely amphoteric with an isoelectric point at about pH 10 8 in buffers of 0 02 ionic strength, whereas a highly purified oxytocic preparation which is also amphoteric, has an isoelectric point in the region of pH 8 5

Physiology of the Neurohypophysial Principles

Elaboration of the Antidiuretic Substance by the Pituicytes

The known distribution of pituicytes in the neurohypophysis coincides exactly with the regions in which the antidiuretic substance has been localized by comparative anatomical physiological and pharmacological investigations That the active antidiuretic substance is not derived from the adenohypophysis was disclosed by studies of the hypophyses of the armadillo, chicken sea cow and whale[6 51 3 4 5] The glands of these *animals are particularly adapted* to such

ber of secretory pituicytes are destroyed suddenly Such a situation can be precipitated by subtotal neurohypophysectomy or by a piqure of the hypothalamus *which interrupts the innervation and thus the function* of a comparable number of pituicytes If there is sufficient secretory tissue left to engage in compensatory hypertrophy and this process must be going on during the so-called latent period the third phase of permanent polyuria does not occur If on the other hand compensatory hypertrophy fails to make up for this deficiency there supervenes a state of permanent polyuria which is due to an absolute insufficiency In this conception the latent period represents a phase during which compensatory metabolic adjustments occur The initial relative insufficiency may be compensated for by one of several mechanisms which would come into play during the latent period (a) reserve supplies of pitressin may continue to be secreted (b) the pituicytes may continue to function at a lower level after having been damaged partially by incomplete denervation (c) the pituicytes which are undamaged or remain innervated may hypertrophy (d) complete atrophy and absolute functional insufficiency of the pituicytes probably do not occur immediately after bilateral interruption of the supraoptico-hypophysial tracts It must take a few days for complete atrophy of the pituicytes to take place just as in the case of the gonads adrenal cortex or thyroid after hypophysectomy (e) compensatory physiological readjustments occur in other aspects of the body economy which have *to do with water exchange e g thyroid liver pancreas adrenal cortex etc* Thu the latent period represents a phase during which compensation for the initial insufficiency occurs If the original damage is extensive enough these compensatory mechanisms cannot obviate the development of an absolute deficiency of pitressin i e permanent diabetes insipidus The variability in the development of the experimental syndrome may be attributed to variations in the extent of *initial damage and the success or lack of success of subsequent attempts on the* part of the organism to compensate for it

Peripheral Effect of the Antidiuretic Substance and Its Clinical Significance

Burgess Harvey and Marshall[70] and Gersh[71] have demonstrated that the neurohypophysial antidiuretic substance acts directly on the renal tubules especially the descending loop of Henle when injected into an animal with diabetes insipidus The cells of this segment of the renal tubule are stimulated to reabsorb more water from the lumen of the tubules thus resulting in the retention of body water and a decrease in the urinary output The antidiuretic principle appears to reinforce and supplement the mechanism responsible normally for the reabsorption of approximately four fifths of the water that passes through the glomeruli [2]

manent diabetes insipidus results regularly, if the denervation, transection or ablation involves all or a major portion of the neurohypophysis, including the median eminence Magoun, Fisher and Ranson[64] found that the onset of the disease could be prevented in monkeys if as little as 15 per cent of the median eminence remained uninjured Similar results have been recorded in rats[6] and dogs [b] although an equally precise localization has not been possible In the rats polydypsia and polyuria result from ablation of the infundibular process or transection of the infundibular stem at the level of the infundibular process, and the intensity of the disorder increases in severity as the lesion is placed more centrally

Pathological Physiology of Experimental Transient and Permanent Polyuria

Considerable confusion in the interpretation of experimental data has resulted because of the failure on the part of earlier workers to differentiate between per manent polyuria which represents true diabetes insipidus, and the transient type, which does not

After the operative procedure, which is employed ordinarily to damage the hypothalamus there is a transient state of polyuria lasting about one week This is succeeded by a few days of normal fluid exchange Within 10 or 12 days after operation, however there appears the third or permanent phase of polyuria, which reaches its peak within two to three weeks postoperatively The time extending from the day of operation to the day of the onset of the permanent polyuria is referred to as the latent period[60] Most hypothalamic operations of the type which induces bilateral destruction of the supraoptico hypophysial tracts, are fol lowed by these three phases of disturbance in water balance[58] It has been ob served also that experimental diabetes insipidus may develop gradually over a period of 2 to 3 weeks before reaching its peak Heinbecker and Clark[68] have demonstrated however that the third phase of permanent polyuria may be achieved immediately after operation, if all of the neurohypophysial tissue is de stroyed These studies indicate that the extent of the damage to the secretory parenchyma of the neurohypophysis determines the subsequent course of the ex perimental syndrome There have been many theories concerning the physiologi cal significance of this sequence of events So far as this writer can interpret the evidence it indicates that the first phase of water disturbance is due to a state of relative insufficiency of pitressin and that the third phase represents a condition of absolute insufficiency Ordinarily the organism has at its disposal certain reserve supplies of pitressin which contribute to the regulation of water metabolism in response to emergency demands e g dehydration A relative insufficiency in the supply of pitressin must occur when a significant proportion of the total num

sponse is not due to adrenalin or sympathin [1] whereas the latter shows that vagal impulses bring about the secretion of the pressor hormone of the neurohypophysis by way of the infundibular stem The pathway of the impulses engendered by vagal stimulation may be assumed from the foregoing as well as the following observations Electrical stimulation of the anterior part of the hypothalamus elicits a similar pressor effect but the reflex vagal pressor response is not obtained if the anterior part of the hypothalamus is damaged so that the connections between the supraoptic nuclei and the lobus nervosus are severed [5, 88] These observations were substantiated by Sattler who found this reflex absent *in animals with experimental hypothalamic diabetes insipidus It may be assumed* from these data that the afferent vagal impulses activate the supraoptic nuclei from whence the stimuli are transmitted to the lobus nervosus via the supraoptico-hypophysial tract That an identical pathway controls the secretion of the pressor and antidiuretic principles is suggested furthermore by correlation of the cytological condition of the pituicytes and the extent of the pressor effect elicited by vagal stimulation Repeated stimulation of the vagus results apparently in a loss of the secretory granules of the pituicytes coincidentally with a diminution of the pressor response Recovery of the pituicytes and reestablishment of the pressor response occurs after the stimulus is discontinued [1]

Evidence on the Neurogenic Secretion of the Oxytocic Substance

That the secretion of the oxytocic principle pitocin is also under the control of a hypothalamic mechanism has been disclosed by the experiments of Fisher Magoun and Ranson and Pencharz and Long Fisher and associates observed a marked disturbance in the parturition of cats afflicted with experimental *hypothalamic diabetes insipidus* Some of the animals died in labor others experienced a greatly protracted labor during which only part of a litter was delivered in some cases The adenohypophysis was found to be functionally intact in these animals Further evidence along similar lines has been recorded by Haterius and Ferguson [4] who showed that electrical stimulation of the infundibular stem enhances significantly the uterine activity of the rabbit in the post partum period This effect is abolished by transection of the infundibular stem but is not obviated by vagotomy splanchnicotomy or transection of the spinal cord

The atrophy, physiological inactivation or surgical destruction of the pituicytes is believed to result in a decrease in the concentration of the antidiuretic hormone in the blood. This results in diabetes insipidus, since the normal effect of this hormone on the water reabsorbing mechanism of the descending loop of Henle is interfered with. A disturbance of water metabolism in the opposite direction is induced by deprivation of water. Shortly after the latter is instituted, there is an appreciable decrease in the amount of antidiuretic substance stored in the infundibular process of the guinea pig, rabbit or rat[10, 3, 4] and a coincidental hypertrophy and hyperplasia of the pituicytes[10]. Other studies indicate that these physiological and cytological changes are paralleled by an increase in the concentration of the antidiuretic principle in the circulating blood[1] and urine[49] of the rat.

Central Effect of the Antidiuretic Substance and Possible Clinical Significance Thereof

There is another aspect of the physiological activity of the antidiuretic hormone which is less clearly understood. This is its so called central effect which was demonstrated by Cushing[6] and Molitor and Pick[77] who observed a relatively stronger antidiuretic effect when the hormone was administered directly into the third ventricle or into the cerebellomedullary system. Other experiments seem to indicate furthermore that the antidiuretic activity of this hormone is inhibited by transection of the upper portion of the cervical cord[8, 79]. These experimental observations are in accord with certain clinical data, viz. the relative therapeutic superiority of the nasal application of the hormone over that of the parenteral route, and the absence of its antidiuretic action in certain cases of injury to the tuber cinereum or to the posterior region of the thalamus. Pathological changes with destructive lesions in these areas have been suggested in explanation of some of those rare instances of diabetes insipidus, which are partially or wholly refractory to the antidiuretic hormone[6, 80, 81, 8, 83].

Neurogenic Secretion of the Pressor Substance by the Pituicytes

In view of the possibility that the neurohypophysial hormone is a protein mother molecule from which three active principles may be separated by chemical means, it is significant that the same neurological mechanism seems to be concerned with the secretion of each of these various biologically active substances. The reflex vagus pressor response is elicited by afferent vagal impulses in animals subjected to transection of the cervical spinal cord but fails to occur if the infundibular stem is severed. The first observation indicates that the pressor re

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CHAPTER XV

DISEASES OF THE PARATHYROID GLANDS

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Structure and Functions of the Parathyroid Glands

Anatomy

The parathyroid glands are small bodies lying in close proximity to the thyroid. Their number is highly variable ranging from one to eight and even as in Erdheim's[48] case to twelve. Usually there are four arranged in two pairs. The superior or internal pair lie on the medial aspect of the dorsal surface of the thyroid at the junction of the upper and middle thirds of each lateral lobe. Although they ordinarily rest on the capsule of the thyroid gland, they may be imbedded sometimes in its substance. The inferior pair, also known as the external glands, likewise are on the dorsal surface farther down and closely associated with the inferior thyroid veins and the esophagus. When there are more than four parathyroid glands the accessory tissue may be scattered widely. As demonstrated by Ferry[136] it may be found on the anterior surface of the thyroid

It may be either in the anterior or posterior mediastinum or even imbedded in the thymus The size of the glands also is variable Cowdry[50] has stated that normally they may have measurements of 6 x 3 x 2 mm and a combined weight of 550 mg Biedl[14] has considered 3 to 15 x 2 to 4 mm as the limits of normal dimensions In the same individual the glands differ greatly in size

The blood supply of the parathyroids comes from both superior and inferior thyroid arteries and is very abundant It is returned through a venous plexus The innervation which seems to be scant comes from the perivascular sympathetic

Study of the minute anatomy of the glands has revealed densely packed columns and clumps of cells between which is a framework of connective tissue and a richly anastamosing network of capillaries Two types of cells have been recognized The chief cells have a relatively large vacuolar nucleus and pale cytoplasm which seldom contains granules The oxyphile cells are larger with small deeply staining nuclei and with granular cytoplasm readily stained by acid dyes It is said that before the age of ten only chief cells are found in human parathyroids[106]

Functions

It required many years and the work of a large number of observers to establish the importance and the various functions of the parathyroid glands The questions involved perhaps can be appreciated best by a brief account of the successive steps by which our present knowledge has been obtained The external parathyroid glands were described and named in 1880 by Sandstrom[125] and independently a year later by Baber[4] It is interesting that at almost the same time Weiss[152] in Billroth s clinic at Vienna found that the operation of thyroidectomy might be followed by serious and often fatal symptoms which were identical with the clinical condition known as tetany These two observations were not correlated Both Sandstrom and Baber believed that their newly discovered bodies were composed of embryonic thyroid tissue Their work attracted little attention and many years passed before the functional importance of the parathyroid tissue was realized It was indeed eleven years later that Gley[63] of Paris apparently unaware of the description of either Sandstrom or Baber rediscovered the glands He also considered that they were composed of thyroid tissue but was convinced by his experiments that they bore an important relation to the fatal symptoms which sometimes followed the complete extirpation of the thyroid gland

Gley was handicapped by his ignorance of the existence of the internal parathyroid glands which were described first by Kohn[83] four years later Without this knowledge the irregular results which followed thyroidectomy were difficult to interpret Kohn s discovery may have aided Vassale and Generali[140]

who demonstrated that removal of all parathyroid tissue even with preservation of the thyroid caused the death of an animal while the removal of the entire thyroid was not necessarily fatal if only one parathyroid was preserved They also showed that preservation of the parathyroid tissue did not prevent cretinism or myxedema With such experiments they were able to differentiate clearly between the functional characteristics of the two glands They showed also that the parathyroid glands were vital structures the removal of which was followed in 24 to 36 hours by changes in the excitability of nerves and muscles by twitchings stiffness and spasms which resulted in death in from five to ten days Except for this thoroughly demonstrated fact, the functions of the parathyroids still remained quite obscure

Investigations from this time followed two main hypotheses (1) that the parathyroids are important in the removal of toxins and particularly of the split products of protein, (2) that the glands are intimately associated with the regulation of mineral metabolism

Detoxifying Function of the Parathyroid Glands — Vassale and Generali attempted to explain the fatal symptoms of tetany by assigning to the parathyroids a detoxifying function It has been observed that a diet abundant in meat hastened the onset and increased the severity of the symptoms, also that parathyroidectomy was more fatal in young dogs and in pregnant animals in whom the metabolism was presumably high Biedl[34] noted that bleeding and transfusion of normal blood exerted a beneficial effect, while MacCallum[95] showed that the removal of blood and replacement with normal saline solution caused prompt relief of symptoms These observations seemed to lend support to the idea that tetany might be associated with a cumulative toxemia which might be due to split products of protein This hypothesis was followed with enthusiasm and for a time experiments seemed to furnish evidence of a detoxifying function Koch[67] believed that he could demonstrate methyl guanidine, a product of endogenous protein metabolism, in the urine of dogs after parathyroidectomy In a series of experiments Paton[113] showed that the symptoms produced by guanidine and methyl guanidine were identical with those which appear following thyroidectomy that small doses of these substances aggravated the symptoms of tetany, and that both guanidine and methyl guanidine were found in the urine and blood of parathyroidectomized animals These encouraging results did not, however long remain unchallenged It was realized by Paton himself, that the chemical methods available for the determination of guanidine in the blood and urine were unsatisfactory With an improved method Greenwald[68, 69] was unable to show any increase of these substances A closer analysis moreover, revealed that although there is close similarity between the symptoms produced by tetany and by chronic guanidine poisoning they are not identical

Recently the investigation of the detoxifying activity of the parathyroids,

while perhaps not entirely abandoned has received comparatively little attention The need of such an hypothesis to explain the origin of tetany has been removed largely by study of the changes in calcium metabolism which occur after parathyroidectomy

Functions of the Parathyroid Glands in Mineral Metabolism — It was shown by Sabbatini[1-4] that the injection of sodium citrate or sodium oxalate salts which precipitate calcium caused an increase in the excitability of nerve tissue and that the administration of calcium exerted a quieting effect Jacques Loeb[92] observed that the injection of any salt which precipitated calcium and diminished the amount of calcium in the circulating blood and fluids of the body caused twitching These experiments suggested that a lack of calcium in the body might be an important cause of the symptoms following parathyroidectomy MacCallum and Voegtlin[95] investigated the calcium metabolism of dogs after complete extirpation of the thyroids and parathyroids In the tetany thus produced they found a reduction in the calcium content of the blood amounting sometimes to as much as 50 per cent of the total Later MacCallum Lambert and Vogel[96] performed other important experiments using Abel s dialysis apparatus They perfused blood against an artificial fluid containing all the inorganic diffusible constituents of the blood except calcium and thus rid the blood of a large part of its calcium content This dialyzed blood deficient in calcium was perfused through an isolated extremity and produced excitability of nerves entirely similar to that observed after removal of parathyroids Luckhardt and Goldberg[93] and Salvesen[1-6] showed that parathyroidectomized dogs can be kept free from symptoms when sufficiently large amounts of calcium are administered

Following parathyroidectomy there is an immediate decrease in the phosphorus excreted in the urine followed by a rise in the level of serum phosphorus With this rise there is an almost simultaneous fall in serum calcium and a subsequent diminution of calcium excretion[2] Greenwald[66 67 70] has emphasized that the decrease in phosphorous excretion is much greater than can be accounted for by accumulation of phosphorus in the blood indicating a retention elsewhere in the body Bulger Dixon and Barr[30] found similar changes in a case of tetany which developed after removal of a parathyroid tumor

Parathyroid Hormone — By 1924 it was thoroughly established that removal of the parathyroid glands produced a hypocalcemia that this could be corrected and that tetany could be controlled by the administration of calcium It was during this year that Collip[38] presented final proof that properly prepared extracts of the parathyroid glands contain an active principle which uniformly relieves the symptoms in parathyroidectomized animals This can be accomplished even in young dogs kept on a meat diet the conditions which are most favorable to the development of fatal symptoms Collip also showed an elevation of the calcium content of the blood and a greatly increased excretion of calcium

who demonstrated that removal of all parathyroid tissue even with preservation of the thyroid, caused the death of an animal, while the removal of the entire thyroid was not necessarily fatal if only one parathyroid was preserved. They also showed that preservation of the parathyroid tissue did not prevent cretinism or myxedema. With such experiments they were able to differentiate clearly between the functional characteristics of the two glands. They showed also that the parathyroid glands were vital structures, the removal of which was followed in 24 to 36 hours by changes in the excitability of nerves and muscles, by twitchings, stiffness and spasms which resulted in death in from five to ten days. Except for this thoroughly demonstrated fact, the functions of the parathyroids still remained quite obscure.

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operations for recurrence in Graves disease where scar tissue and adhesions have distorted the normal landmarks Tetany has been seen occasionally after laryngectomy for cancer when removal of surrounding structures has been unusually thorough

It may appear either because all of the parathyroid tissue has been removed a relatively uncommon occurrence because of the wide distribution of parathyroid tissue in man or because of interference with the blood supply Occasionally the vessels may be tied too completely at the time of operation More frequently they become obliterated gradually by fibrous tissue adhesions and contraction of scar tissue In such instances the symptoms of tetany may appear for the first time six weeks to two months after the operation

General — Parathyroidectomy is only one of the many causes of tetany The great variety of etiological relationships have been emphasized by Frankl Hochwart[61] in his elaborate monograph He showed that while the condition is met with at all periods of life it occurs most frequently in infants and young adults He also demonstrated the striking seasonal variation in its incidence and its surprising prevalence during the cold months from January to April His review revealed its relation to maternity especially to the late months of pregnancy and the period of lactation He also described and gave numerous examples of the occurrence of tetany in apparent epidemics in certain occupations in association with gastric and intestinal disorders accompanying or following infections and intoxications and associated with a variety of nervous diseases

Although none of these forms of tetany can be attributed directly to a lack of function of the parathyroids they are important because of the light which they cast on the pathogenesis of tetany and because any one of them may complicate the tetany of parathyroid origin or may indeed act as the precipitating cause of individual attacks

So called Epidemic Tetany — The incidence of tetany has varied greatly in different countries and cities In Vienna and Heidelberg there was for many years a prevalence so great as to suggest an epidemic character Particularly notable were the outbreaks in Vienna Young men between the ages of 17 and 25 were attacked by a tetany which occasionally was accompanied by fever and which subsided in two to three weeks Most astonishing was the incidence among workers in certain occupations In 399 cases collected from the literature by Frankl Hochwart 174 occurred in shoemakers and 95 in tailors Only 19 cases were seen in women The seasonal incidence was striking also a great majority of the cases appearing during the cold months and particularly in March and April Each year from August to October the condition disappeared almost entirely

It is significant as pointed out by Barker[7] that in the so-called epidemics of

in the urine Administration to normal individuals, moreover, produces hypercalcemia and a condition which in many respects is the exact opposite of tetany When it is continued in large doses, it is followed by serious consequences Large amounts of calcium are removed from the skeleton with deposit in the kidneys lungs and stomach Still larger doses cause violent toxic symptoms with congestion and hemorrhage in the gastrointestinal canal, cessation of renal function and death[45]

TETANY

Definition — Tetany is a condition characterized by hyperexcitability of the nervous system and by continuous or intermittent spasm of muscles It follows the removal or functional insufficiency of the parathyroid glands but is associated also with a great number of clinical conditions which, to superficial examination appear unrelated While it is convenient to consider tetany as a separate disease it is in reality, a physiological response of nerve and muscle tissue which appears inevitably whenever certain disturbances in calcium metabolism or acid base equilibrium occur in the animal organism

History

The development of our knowledge of tetany has been reviewed interestingly by Barker[-] It appears that Clarke[43] in 1815 was the first to record the clinical features of the condition In discussing spasm of the glottis in children he called attention to the rigidity of the extremities which accompany it The name of tetany was given by Lucien Corvisart[49] who wrote a thesis on the subject in 1852 Erb[7] made his careful studies of the electrical hyperexcitability of the motor nerves in 1874 and the elder Chvostek[42] in 1876 described the facial phenomena which still bear his name About 1880 great interest was aroused in Vienna by a prevalence of tetany which assumed almost epidemic proportions At this time it was first noted by Weiss[14] that the clinical picture of tetany occasionally appeared after operations for the removal of goitre

Etiology

After Thyroidectomy — In the early days of the operation tetany was seen most often in those cases in which complete thyroidectomy was performed for the removal of huge simple goitre It is now encountered after complete removal of the thyroid for carcinoma of the gland but more often as an accident after subtotal thyroidectomy in cases in which the posterior capsule has not been conserved sufficiently It is particularly liable to occur after secondary

operations for recurrence in Graves disease where scar tissue and adhesions have distorted the normal landmarks Tetany has been seen occasionally after laryngectomy for cancer when removal of surrounding structures has been unusually thorough

It may appear either because all of the parathyroid tissue has been removed a relatively uncommon occurrence because of the wide distribution of parathyroid tissue in man or because of interference with the blood supply Occasionally the vessels may be tied too completely at the time of operation More frequently they become obliterated gradually by fibrous tissue adhesions and contraction of scar tissue In such instances the symptoms of tetany may appear for the first time six weeks to two months after the operation

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tetany, patients, before the onset of contractures, had complained of paresthesias the actual spasms which led to the diagnosis appearing only under the influence of some infection, gastrointestinal upset or psychic trauma It was found also that some of the patients affected by seasonal tetany had suffered from laryngeal spasm or convulsions common manifestations of tetany in infancy

Tetany in Children — The study of tetany in children has emphasized many of the most important etiological factors It occurs chiefly during the winter months It is most prevalent among the lower classes and particularly in debilitated children The evidences of rickets are seldom absent Occasionally it may follow prolonged infections and more especially illnesses characterized by persistent diarrhea or excessive vomiting Gastric dilatation from obstruction of the pylorus is a frequent cause

Tetany in Pregnancy and Lactation — Trousseau[138] first described tetany in nursing mothers and gave to it the name of nurse's contracture' It is rare during the first months of pregnancy, at the time of labor or in the puerperium It appears usually in the latter half of pregnancy and may occur in the same individual with successive pregnancies, the interval being free of major attacks In the 52 cases collected by Frankl Hochwart, 39 occurred between January and April Children born of mothers with tetany may themselves exhibit the condition either immediately after birth or later

Tetany in Diseases of the Digestive Tract — Kussmaul[90] in 1869 writing of dilatation of the stomach recorded associated tonic spasms of the extremities This condition ordinarily due to stenosis of the pylorus, is known as *gastric tetany* It has been seen with the congenital pyloric stenosis of infants with the scars of old gastric or duodenal ulcers with peripyloric adhesions and cancer of the stomach It may occur from a dilated proximal pouch with hour glass contraction of the stomach It is interesting however, that only a relatively small number of patients who develop gastric dilatation ever show signs of tetany

Prolonged diarrhea often has been followed by muscular spasms both in children and in adults It has been described in association with sprue and in other diarrheas characterized by steatourhea[35, 80]

Tetany in Infections — Tetany is rare in acute infections although isolated examples of its occurrence have been recorded in a great number of diseases It has been observed most frequently perhaps after the long debilitating course of typhoid It has appeared usually in individuals who have been subject to attacks of tetany previous to the infection and has been seen most frequently in the winter months and in those localities where tetany is prevalent The circumstances clearly indicate that the infection furnishes only an exciting cause in a person who already is predisposed

Tetany in Nervous Disorders — More significant perhaps are the examples of tetany which have accompanied severe pain fear or other violent emotions

in hysterical or nervous individuals This form by no means is infrequent Anxiety preceding an ordeal such as an operation may be sufficient to produce it It is seen often in the early stages of anesthesia In hysteria and in epilepsy it has occurred during phases of excitement Tetany has also been seen during paroxysmal hyperpnea in patients convalescent from lethargic encephalitis [4]

Pseudohypoparathyroidism — Albright has called attention to a syndrome in which the clinical findings are those of idiopathic hypoparathyroidism but in which evidence suggests that the disturbance is not a lack of the hormone but a resistance to it Serum calcium values are depressed and serum phosphorus is greater than normal but the abnormal chemical findings fail to respond to the administration of parathyroid extract Study of the urine fails to reveal the usual response of phosphate diuresis following the administration of parathyroid extract[19]

Physiological Basis of Tetany

The multiplicity of etiological factors has introduced great difficulty in our understanding of tetany and for a long time it seemed impossible to present a unified explanation of all the apparently conflicting observations Our knowledge has been greatly advanced by the establishment of two fundamental facts

1 That there is a profound disturbance of calcium metabolism not only following parathyroidectomy but also accompanying several other forms of tetany

2 That changes in the acid base equilibrium of the body exert a controlling influence upon the excitability of nerves and muscles

Hypocalcemia in Tetany — The changes in calcium metabolism occurring after parathyroidectomy have been discussed already Hypocalcemia has been seen also in other forms of tetany in rickets in sprue in persistent diarrheas and in pregnancy

In none of these forms is there evidence of anatomical defect or functional insufficiency of the parathyroid glands Indeed in rickets considerable hyperplasia of the parathyroids usually is demonstrable Other explanations must be sought to explain the diminished blood calcium In pregnancy and lactation hypocalcemia appears to depend upon the great losses of calcium from the mother in the formation of the child A similar situation has been observed in the milk fever of high bred cows after calving A constant loss of calcium may be the ultimate explanation of hypocalcemia in long standing diarrhea The pathogenesis of the defect in rickets has been elucidated by the pediatricians who show the detrimental effect of lack of sunlight and insufficient content of vitamins in the diet Although none of the so-called epidemics of tetany have been studied from the standpoint of calcium metabolism it does not seem unlikely

that in these also hypocalcemia may be a feature and that food factors and lack of sunlight may play an important role in the greater prevalence of the disease during the winter months and the high incidence among tailors and shoemakers whose work keeps them throughout the year from exposure to direct sunlight

From these observations, one must conclude that whatever the cause of hypocalcemia may be, the result is hyperirritability of muscle and nerve tissue Since, in a number of the more important forms of tetany hypocalcemia is a striking feature, it is fair to assume that, in these cases, lowered calcium content is the controlling influence in the production of tetany This explanation does not, however account for many other examples of tetany which clinically cannot be differentiated from the hypocalcemic form

Acid base Equilibrium in Tetany —Our knowledge of tetany was aided greatly by an observation of Grant and Goldman[65] in Erlanger s laboratory They showed that tetany could be produced voluntarily in normal individuals by forced deep breathing By such overventilation carbonic acid is removed from the body to such an extent that the reaction of the blood and tissues become notably more alkaline In an experiment in which the subject breathed as deeply as possible at the rate of 14 per minute the reaction of the blood had changed in 25 minutes from pH 7 4 to pH 7 9 and spasms of hands and feet had appeared

It has been demonstrated since by Harrop[71] and by Healy [5] that the administration of sodium bicarbonate in amounts sufficient to alkalinize the blood may produce severe or even fatal tetany McCann[98] had suggested already in 1918 that gastric tetany might be due to the failure of the acid gastric secretion to pass into the duodenum

The production of tetany by means of increased alkalinity explains also the spasms which so often occur during the stage of early anesthesia and with pain fear or anxiety It is probably the cause of the occasional appearance of tetany in hysteria and epilepsy and certainly of its occurrence in the paroxysmal hyperpnea which follows epidemic encephalitis

Relation of Hypocalcemic Tetany to the Tetany of Increased Alkalinity — It is significant that the cases of tetany characterized by hypocalcemia may show little or no change in the alkalinity of the blood and that on the other hand, the patients with most marked alkalinity may exhibit an almost entirely normal calcium content The question arises whether these two types represent two entirely different causes for tetany or whether they may be in some way related It is known that the degree of ionization of calcium salts in the blood is dependent upon its alkalinity and that within the limits of change in the body the more alkaline the body fluids become, the less is the degree of calcium ionization The evidence indicates that the physiological functions of nerve and muscle are dependent upon the concentration of calcium ions, the value of which can be

diminished either by a reduction in the total amount of calcium in the blood (hypocalcemia) with normal alkalinity or by increased alkalinity with normal total calcium content It has been suggested therefore but without convincing evidence, that the tetany of alkalosis is in reality dependent upon reduction in the values of ionized calcium in serum and tissue fluids

The two factors may be combined temporarily or continuously in the same case and act upon each other to aggravate symptoms or precipitate attacks In parathyroid tetany spasms may be induced by voluntary overventilation Following complete removal of the parathyroids the violent attacks sometimes have been ushered in by periods of extreme hyperpnea Hysterical or highly emotional patients who are liable to spells of overbreathing may have been subjected to repeated pregnancies and prolonged periods of lactation or may have received insufficient sunlight and inadequate diet

Pathology

Pathological study of the parathyroid glands has been greatly hampered on account of their small size their hidden position the difficulty of their recognition and also because they are seldom examined during a routine autopsy Acute inflammation of the parathyroid glands themselves is unusual They have been involved by extension of inflammatory disease in surrounding tissues but in these instances symptoms of parathyroid insufficiency have not made their appearance In generalized tuberculosis and syphilis involvement of the parathyroids has occurred but has been unsuspected clinically and discovered for the first time at the post mortem examination

Hemorrhage into the parathyroid glands has been observed several times in patients who had died of infantile tetany The extravasation of blood has been of all grades from slight local leakage to extensive infiltration and obliteration of functional tissue Hemorrhages have been seen also in cases where tetany has not been noted clinically In the case of idiopathic tetany reported by Drake autopsy revealed fat replacement of all parathyroid tissue[54]

General Symptoms and Signs

The subjective and objective manifestations of tetany are always of the same general character whether they follow parathyroidectomy or voluntary forced breathing whether they are dependent upon a diminished amount of calcium in the blood or upon an increase in alkalinity The majority of the symptoms and signs of tetany are referable to the hyperexcitability of the nervous system While the motor nerves are involved most obviously the participation of the sensory apparatus is evidenced by parasthesias or pain and of the autonomic by

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Fig 2 A Photograph of patient with latent tetany following parathyroidectomy B Same patient showing typical facies in an attack induced by voluntary forced breathing

an abnormal sensitiveness to epinephrin and pilocarpin Differentiation should be made between *manifest tetany* in which the hyperexcitability is so great that intermittent attacks of muscular spasm occur spontaneously, and *latent tetany* in which no spontaneous motor phenomena are seen and which can be recognized only by special examinations



Fig 1 Complete left carpal spasm and stiffness of right hand in parathyroid tetany

Muscular Spasm —Attacks of tetany usually are preceded by parasthesias such as tingling or numbness of the fingers or lips There is often a feeling of anxiety and depression More rarely there may be headache vomiting or pain in the back Fibrillary twitching of the muscles is a frequent premonitory sign The spasms most often start in the hands and next involve the feet. They may, however, start in the muscles of the trunk or even in the facial muscles Usually the affection is symmetrical but it may involve one hand without being manifest elsewhere rarely it may be unilateral involving the arm and leg of one side and still more uncommonly it may be seen in the arm of one side and the leg of the

It has been observed that when a moderate spasm has been overcome by force a more powerful and violent after spasm may follow

Excruciating cramp-like pain may accompany the spasms in severe cases It usually appears and subsides with the contraction and in some cases may have an intermittent character when the contractions appear to be continuous Either direct pressure on muscles nerves and joints or movements of the muscles may cause great discomfort

During sleep the attacks of tetany usually are diminished but on the other hand occasionally they may appear for the first time in sleep

Mechanical Irritability of Nerves and Muscles — A great number of external stimuli have been observed to induce spasms of tetany in susceptible individuals. The administration of enemata a gastric lavage percussion of the abdomen pressure on muscles or nerves and temporary interference with the circulation of an extremity are among the many causes which have been mentioned Some of these are of such a striking character that they have been utilized in the clinical recognition of latent cases

Trousseau[139] pointed out in 1864 that if in latent tetany a tourniquet is applied firmly about the upper arm so as to suppress the flow of blood through the artery an obstetrical hand could be produced in a few minutes This is usually known as *Trousseau's sign* ' Three minutes or more of pressure may be necessary to elicit the sign even in susceptible individuals It is probably demonstrated best by the use of a blood pressure cuff The exact mechanism underlying this phenomenon has been under dispute The excessive irritability of nerves in tetany is admitted but it has been shown also that the excitability of nerves may be greatly exaggerated by partial anoxemia[109] Since the application of a tourniquet exerts pressure both on nerves and blood vessels it seems probable that both factors are concerned Frankl Hochwart s experiment[61] however seems to indicate that pressure on the nerve is entirely responsible He found that the slightest pressure applied to the exposed nerve of a parathyroidectomized dog caused spasm while even the strongest pressure upon the blood vessels was without effect When Trousseau s sign can be elicited it is a valuable diagnostic aid It is absent however in many undoubted cases of tetany

Chvostek s sign may be demonstrated in the interval between acute attacks and also in latent tetany It consists of a localized spasm produced by percussion over a muscle or nerve Although this hyperirritability may be demonstrated in any part of the body usually it is shown best along the course of the facial *nerve by tapping either at the stylomastoid foramen or on the cheek The sign* may be seen in many patients who at the time present none of the other manifestations of tetany Unfortunately from a diagnostic standpoint it has been observed occasionally in Graves disease in tuberculosis and even in otherwise entirely normal individuals'

other Many serious disturbances have been recorded Ordinarily when the trunk muscles are included in the spasm, those of the ventral aspect of the body are affected chiefly The head is bent forward, the sternomastoids are prominent and the chin may be drawn down until it touches the sternum If one sternomastoid is affected without the other, an appearance of torticollis may be produced Rarely the back muscles are affected more than the ventral group causing an opisthotonus which may be confused with tetanus In cases showing general involvement the diaphragm may become involved causing serious interference with respiration The tongue not uncommonly is included and causes a thick speech Strabismus may be a prominent and troublesome symptom In children and occasionally in adults the muscles of the larynx are involved giving rise to laryngismus stridulus or croup

While any muscle may be affected and the vagaries of involvement are considerable, certain types of contraction occur so frequently that they must be given special emphasis and description

Carpopedal spasms are seen in many rachitic infants in whom other evidences of the condition never become manifest Usually they are the earliest and probably are the most constant of the major phenomena in adult forms of tetany (Fig 1) In the hand the thumb is adducted in close contact with the index finger or flexed into the palm beneath fingers which are flexed in the metacarpophalangeal and extended in the interphalangeal articulations The outer and inner borders are approximated producing a *hollowing of the palm The shape* of the hand resembles so strikingly that which the obstetrician employs in his examination that it was called by Trousseau the 'main de l accoucheur' Other attitudes of the hand may be encountered but rarely Mention may be made of the hand which assumes the shape of a bird s claw, of that which is flexed in all *its joints producing a tightly closed fist and a contracture which may* be so marked that the fingernails cause necrosis of the palm, and of the extremely uncommon attitude in which all the fingers are spread wide apart and extended

The pedal spasm usually consists of powerful flexion and adduction causing extreme arching and concavity of the sole The foot is extended at the ankle and inverted Russell[123] states that dorsal flexion of the foot at the ankle has been observed

When the spasms become general, the face is involved Often this is limited to a feeling of stiffness about the mouth and to a fibrillary contraction or twitching of the muscles at the corners of the mouth In more severe cases the face is contorted into a ghastly grin in which the eyes are closed and the angles of the mouth are drawn up and outward (Fig 2)

During the spasms the muscles are hard and firm, and considerable force is necessary to release them This may be noted by the patient, as when a porter carrying suitcases finds himself quite unable to release his grasp on the handles

have completely formed there is hypoplasia which leaves its scars in the tooth structure as pit like depressions extending horizontally across the surface If the disease develops after the age of twelve the tooth structure may be normal except for blunting of the root ends and hypoplasia of the last teeth to form

Bilateral cataracts tend to form in all cases of long standing Usually these are subcapsular opacities which can be detected only with the slit lamp In other cases however there is transformation of both lenses into gray white masses which require surgical removal for the restoration of eyesight

Prognosis

Fortunately complete removal of parathyroid tissue in man always has been infrequent Many of the patients who formerly developed tetany after thyroid operations made a more or less complete recovery although latent tetany and nutritional disturbances often persisted In those rare cases where the parathyroids were entirely extirpated death was inevitable from the violent symptoms which appeared immediately after the operation Those who retained some but insufficient parathyroid tissue had a miserable existence in which a constant tendency to seizures precluded all normal activity and led to pitiful anxiety or profound depression With our present methods of treatment patients may survive even complete parathyroidectomy and if calcium is maintained at a normal level in the serum may escape the discomforts and the serious trophic disturbances of chronic hypoparathyroidism

Treatment

General — The treatment of tetany varies greatly with the underlying cause and with the mechanism involved To control the spasms in cases dependent upon hypocalcemia and disturbed mineral metabolism the chief efforts must be directed to an attempt to increase the content of calcium in the circulating blood For patients whose tetany is the accompaniment of increased alkalinity measures devised to change the reaction of the blood should be most effective In cases associated with disturbance of calcium metabolism the initial cause of hypocalcemia is of great importance When it has developed from lack of sunlight or an insufficient intake of vitamin D administration of these agents in moderate amounts may be sufficient to remove the tendency If it is dependent upon absence or insufficiency of the parathyroid glands parathyroid hormone or very large doses of vitamin D or both may be required in the management of the acute attack During maternity and in continuously undernourished individuals a supply of extra calcium sometimes is quite as significant as an increase in vitamin content It should be remembered that several different factors may be of importance in the same case as when overventilation occurs with hypocalcemia or

Other tests, depending upon the mechanical irritability of nerves have been described by Pool[117] and by Schlesinger[127] They consist of the production of carpal spasm by forcible abduction of the arm and of pedal spasm by flexion of the trunk upon the thighs with legs extended They probably parallel the positive response to Trousseau's sign and in general have the same significance

Electrical Irritability of Nerves and Muscles — Erb[67] of Heidelberg was the first to demonstrate the utility of electrical excitability as a diagnostic test in tetany It has been studied since quantitatively and with great care by von Pirquet[115] and many others The chief abnormality in tetany consists of a response to a current much smaller than that required to stimulate a normal individual In children cathodal opening contractions are apparent with a current usually much less than 5 milliamperes which is considered the least which will stimulate normal nerves By von Pirquet anodal opening contractions with currents feebler than 5 milliamperes have been considered also indicative of mild tetany These electrical tests, when performed with experience and judgment have been of great aid in the recognition of latent tetany in children

Reflexes in Tetany — Considering the extreme hyperexcitability of muscles and nerves exaggeration of reflexes might be expected It is surprising that this does not occur with any regularity The knee jerks are normal in some cases, exaggerated in others and may be greatly diminished or actually not obtainable

Mental and Nervous Symptoms — The state of chronic tetany not infrequently is associated with profound anxiety and depression or by a sense of impending disaster Frankl Hochwart[61] collected examples of the occasional occurrence of psychopathic symptoms varying from transitory delirium during the individual attacks to confusion and actual dementia

Epilepsy or epileptiform attacks have developed not infrequently in tetany The cases collected by Redlich[119] indicate that the association of the two conditions is not limited to any particular form of tetany The convulsions have been seen not only after thyroidectomy but also in association with maternal and gastric tetany They are most frequent in the tetany of young children and with long continued hypocalcemia Very rarely chronic tetany has been accompanied by papilledema engorgement of retinal veins and increased cerebrospinal pressure of a degree to suggest the presence of brain tumor[31]

The mechanism of the nervous symptoms is not clear Edema of the brain itself[1] or increase in cerebrospinal fluid has been suggested Of great interest is the symmetrical calcification of basal ganglia and other parts of the brain which has been demonstrated by Eaton[65] and others[18]

Other Manifestations — Falling nails and loss of hair have been mentioned as consequences of hypoparathyroidism[78] More established are enamel defects of the teeth, which occur both in experimental tetany and in long continued hypocalcemia in man When hypoparathyroidism develops before the teeth

accomplishes an elevation in the level of blood calcium depending upon the size of the dose and the condition of the patient Following subcutaneous or intramuscular injections the serum calcium begins to rise in about 4 hours reaches its maximum in from 12 to 18 hours and returns to the previous level in about 20 to 24 hours It has been shown that the first demonstrable effect of the hormone is an immediate increase in the phosphorus excreted in the urine the second effect is a fall in the level of phosphorus in the serum and an almost simultaneous rise in serum calcium and finally there is an increased excretion of calcium in the urine In not a few patients the subcutaneous use of the preparation produces painful local reactions These consist of red hot areas of induration and edema at the site of injection which usually appear one to two hours after the puncture and gradually disappear over a period of several days Their size varies from an inch to several inches in diameter They are most disturbing factors in those patients requiring frequent injections Tolerance may be acquired and the necessary dose in some cases has become so high as to offer insuperable difficulties in administration and to constitute an unbearable expense to the patient In Lisser s case[91] enormous doses were ineffective finally in controlling symptoms

2 *Calcium Administration* —Luckhardt and Goldberg[93] Salvesen[125] and others showed that parathyroidectomized animals may be kept alive and even in good health if calcium salts are administered in sufficient amounts Immediate relief of the symptoms of acute parathyroid tetany have followed the intravenous use of calcium Clinically three calcium preparations are commonly employed Calcium lactate usually is administered by mouth It is non irritating and may be taken in large amounts the ordinary dosage being 1 0 to 2 0 gm repeated frequently and in severe cases as often as every two hours Calcium chloride also may be given by mouth in dilute solution but it is irritating and apt to cause nausea and gastric distress It cannot be used subcutaneously as it produces intense pain and extensive necrosis Its chief use is as an intravenous preparation which may be administered in doses of 1 0 to 2 0 gm in 5 per cent solution It should be injected slowly because of the toxic effect of high calcium concentration upon heart muscle and with great caution to avoid infiltration of the tissues about the vein Because it is an acid salt it serves when tolerated the double purpose of supplying calcium and of reducing alkalinity The beneficial effect of intravenous calcium chloride upon spasms due to hypocalcemia sometimes is dramatic and almost immediate Calcium gluconate has a similar action and is used more often since it may be given both by mouth as well as by intramuscular and intravenous routes since it is relatively non irritating to tissues and since it possesses many of the advantages of calcium chloride Its dosage is the same as calcium chloride For parenteral use a 5 per cent solution usually is employed

3a *Dihydrotachysterol* — Fortunately the correct use of activation products of ergosterol in the treatment of hypocalcemic tetany has made unnecessary the

when a patient whose parathyroids have been removed by operation is deprived of sunlight and fails to take an adequate diet

Correction of Alkalosis — When tetany follows excessive breathing, whether this be voluntary or the accompaniment of disease there is an increased alkalinity which has resulted from loss of carbon dioxide To correct this the most direct as well as the most effective method is the administration of carbon dioxide in the inspired air In high percentages this gas is toxic and may be dangerous In 5 to 7 per cent mixtures with oxygen it is a powerful stimulant to the respiration but has no deleterious effects Holding the breath will allow carbon dioxide to accumulate in the body and in the control of acute spasms may be all that is required It produces however an anoxemia which in itself increases the irritability of nervous tissue In those cases where overventilation tends to recur or where it is a complicating factor in some other form of tetany, carbon dioxide oxygen mixtures may be inspired through a mask or from a tent Special tanks containing 5 per cent carbon dioxide in 95 per cent oxygen and equipped with reducing valves are now generally available Lacking them, the carbon dioxide may be inspired by means of an extremely simple method A newspaper can be made into a funnel the small end of which is made to fit around the nose and mouth of the patient Air breathed in from this funnel will contain from the last expiration a considerable amount of carbon dioxide the percentage of which will vary up to 4 0 per cent with the volume of the funnel and the snugness with which the funnel is fitted to the face

Another method of diminishing alkalinity is by means of the administration of fixed acids For this purpose the acid salt ammonium chloride is perhaps the most effective drug It can be administered in tablets by mouth in doses of 1 0 to 2 0 grams It is irritating to the stomach if given over any considerable period In animals McCann[98] has given ammonium chloride intravenously in 0 822 per cent solution

Correction of Hypocalcemia — This may be accomplished or aided by the use of (1) parathyroid injection (2) calcium salts and (3) two activation products of ergosterol dihydrotachysterol and calciferol (crystalline vitamin D_2)

1 *Parathyroid Injection* — The active principle of the parathyroid glands can be isolated from the parathyroids of an ox It is obtainable in conveniently and accurately standardized form under the pharmacopeial name of parathyroid injection, one c c of which possesses a potency of not less than 100 U S P parathyroid units each unit representing one one hundredth of the amount required to raise the calcium content of 100 c c of the blood serum of normal dogs 1 mgm within 16 to 18 hours after administration It is inactive by mouth but is active when given subcutaneously or intramuscularly Reactions simulating those from injection of foreign protein and sometimes quite severe have followed its intravenous use The injection is not accompanied by any important sensations but

properly treated may result fatally The situation constitutes an emergency which demands thorough and careful treatment The seriousness of the condition cannot be judged entirely by the character of the spasms Sometimes they yield to the simplest measure such as holding the breath or the administration of carbon dioxide and the subsequent use of calcium by mouth In other cases the underlying state is so severe that its control taxes every therapeutic resource In the emergency chief reliance must be placed on measures which produce prompt effects on the level of serum calcium The action of dihydrotachysterol and calciferol is too long delayed to serve the immediate purpose If the spasms are violent and continue in spite of the administration of carbon dioxide, calcium chloride or calcium gluconate should be given intravenously At the same time parathyroid injection may be given intramuscularly Large doses may be required and 100 to 300 U S P units (1 0–3 0 c c) or even more have been given in severe cases Beneficial effect as evidenced by an elevation of serum calcium usually is apparent within a few hours and reaches a maximum in 8 to 18 hours For maintenance of the level of serum calcium in average adult dose is 20 to 40 units (0 2 to 0 4 c c) every 12 hours Continuation of hormone therapy is however undesirable and an effort should be made to substitute calciferol as soon as possible It is desirable therefore to administer orally 20 to 30 mgm (800 000 to 1 200 000 international units) of calciferol at the same time the parathyroid injection is started This may be repeated every 24 hours until the calcium in the serum has attained a normal level

In the treatment of severe attacks of true hypoparathyroid tetany there is little immediate danger of overdosage either with parathormone or with the derivatives of ergosterol If however the diagnosis is incorrect and the tetany has arisen from causes other than hypocalcemia the possibility of harm from large doses of these extremely potent chemicals is considerable In any case frequent determinations of serum calcium are desirable during the early stages of the management If this is not possible the urine should be tested by the Sulkowitch reagent[14] a solution containing oxalate radicals buffered at such pH that when an equal amount of the reagent is added to urine the calcium will come down almost immediately as a fine white precipitate of calcium oxalate If there is no precipitation by this test the urine contains no appreciable amount of calcium and it may be assumed that the serum calcium does not exceed 5 to 7 5 mgm per 100 c c If there is a fine white cloud there is a moderate amount of calcium and the level of calcium in the serum probably is within a satisfactory range If the precipitate looks like milk there is danger of hypercalcemia The Sulkowitch test is a great aid in the practical management of patients with tetany

After the acute attack has been controlled and the aim of treatment is the establishment and maintenance of normal conditions calciferol is the drug of choice The maintenance dosage must be determined for each individual and

long continued employment of parathyroid injection It had long been known that tetany arising from lack of sunlight and insufficient or improper diet in rickets, pregnancy, lactation and chronic undernutrition could be corrected by the use of cod liver oil Later the same results were obtained by the use of purified preparations of fish oils containing a higher concentration of vitamin D It was disappointing to find, however, that dosage sufficient to correct rickets had relatively little effect upon hypocalcemia from hypoparathyroidism or from any causes other than lack of vitamin D For our knowledge of the usefulness of dihydrotachysterol we are indebted to the work of Holtz[79], who studied with Windaus in Gottingen the effects of various fractions of irradiated ergosterol upon calcium metabolism In the course of his researches he found that three sterols caused definite elevation in the level of serum calcium These were fractions known as tachysterol, toxisterol and the one believed to be vitamin D itself Of these, tachysterol was thought to be least toxic and was rendered still less injurious by the synthesis of a dihydro derivative With small doses of dihydrotachysterol by mouth Holtz found it possible to relieve tetany and to maintain the serum calcium at normal levels in parathyroidectomized animals He also found it effective in the treatment of idiopathic hypocalcemic tetany and in the hypoparathyroidism following thyroid operations The substance was introduced under the name of A T 10 (anti tetany preparation No 10) and became commercially available in an oil solution in which 1 0 c c contained 5 mgm of a basic substance approximately 2 mgm of which was pure dihydrotachysterol This can be given orally in doses of 0 5 to 2 0 c c each day Although dihydrotachysterol alone will raise the serum calcium to normal the amount that is required for maintenance of normal levels of serum calcium is less when calcium salts are used as an adjuvant With an average normal diet daily doses of from 1 to 2 c c are required but when this is supplemented by 4 0 to 10 0 gm of calcium lactate or calcium gluconate each day the dosage can be reduced to 0 3 to 1 0 c c The effect of dihydrotachysterol on serum calcium is not immediately apparent Usually the first increase appears in about 48 hours With small doses normal levels may be expected in most cases of hypoparathyroidism within 7 to 14 days

3b Calciferol — Fortunately it has been found that calciferol (crystalline vitamin D_2) produces the same effects as dihydrotachysterol on the level of serum calcium and consequently upon hypocalcemic tetany when given in equivalent doses McLean[100] found that 1 c c of A T 10 (approximately 2 mgm of dihydrotachysterol) is therapeutically equivalent to 10 mgm (400 000 international units) of crystalline vitamin D_2 This preparation may be given also by mouth Like dihydrotachysterol its action is delayed the first increase in the level of serum calcium usually is not observable before 24 hours have elapsed

Treatment of Parathyroid Tetany — About 24 hours after the removal of an excessive amount of parathyroid tissue symptoms of tetany appear which, if not

thyroidism and by Wilder and others served to indicate the chief features of the condition and to establish a clinical syndrome

Etiology

Hyperparathyroidism may be produced at will by the injection of parathormone as has been demonstrated experimentally in animals It may occur clinically as a consequence of neoplasm or hyperplasia of the parathyroid glands The great majority of the cases occurring spontaneously have been associated with a single adenoma a few with more than one adenoma and a small group reported by Albright and his associates[16] with diffuse hypertrophy or hyperplasia of all parathyroid tissue Albright[17] has reported a case in which persistent low phosphorus rickets was accompanied also by massive calcium deposits in the kidneys hyperchloremia and low serum bicarbonate level A similar situation was recorded by Butler[28] All of these cases may be regarded as examples of *primary hyperparathyroidism* in the sense that the clinical syndrome depends upon an excess of parathyroid activity for which no adequate explanation can be offered Many of them have been accompanied by decalcification of the skeleton and by the deformities of generalized osteitis fibrosa cystica of von Recklinghausen[118] These osseous changes must be regarded as secondary since they may be closely simulated by the skeletal lesions of hyperparathyroidism produced experimentally in animals[84, 85] The primary disease has been observed in young children and in one infant only three months of age[23]

In a great variety of conditions hyperplasia and occasionally tumors of the parathyroids seem to be secondary to changes elsewhere in the body Under such circumstances a state of *secondary hyperparathyroidism* may be said to exist In animals Erdheim[69] found hyperplasia in the artificially produced rickets of rats Marine[104] demonstrated it in fowls which were kept on a low intake of calcium Higgins and Sheard[76] noted it when sunlight was deficient After extirpation of a part of the parathyroid glands there is a compensatory hyperplasia of the remaining tissue Hyperplastic changes were demonstrated by Ritter[112] and later by Pappenheimer and Minot[109] in human rickets MacCallum[94] Bergmann[12] and Albright[7] reported parathyroid hyperplasia in human nephritis More recently the associations of parathyroid function and nephritis have been explored further by Pappenheimer and his associates[110, 111] Apparently hyperplasia of the glands and possibly hyperparathyroidism also develop secondary to diverse skeletal diseases that include not only osteomalacia or adult rickets but also osseous metastases from mammary cancer and multiple myeloma[29] Tumors of the parathyroid glands have been observed also in association with Cushing's disease[107]

The mechanisms by which the parathyroids are stimulated in nephritis are

varies widely From 60 000 to 400 000 international units of vitamin D may be required each day The vitamin will maintain normal levels of serum calcium with an average normal diet, but the dosage often may be decreased 50 to 60 per cent by the addition of 4 to 10 gm of calcium gluconate to the daily intake Milk is to be avoided because of its high phosphorus content Aub[45] has shown that in patients with parathyroprivic tetany, who are receiving adequate intakes of calcium, the use of thyroid tends to cause elevation in serum calcium and to increase the excretion of phosphate The excretion of calcium is augmented after approximately normal calcium levels in the serum have been attained Thyroid in appropriate doses, therefore, may be indicated in parathyroid tetany even in patients who present no striking evidence of hypothyroidism

Hyperparathyroidism

Definition —Hyperparathyroidism is a condition resulting from excessive parathyroid secretion It is accompanied by hypercalcemia, hypophosphatemia, diminished excitability of muscles and changes in the bones, ordinarily it is associated with tumors or hyperplasia of the parathyroid glands

History

Parathyroid tumors and enlargements have been recognized since 1899 when Kocher[53] suggested such an origin for five glycogen containing tumors which he had observed in the region of the thyroid The association of parathyroid tumors with von Recklinghausen s osteitis fibrosa cystica was noted by many observers[4, 61, 78] It was not realized, however that enlarged parathyroid glands might be functionally significant before 1924, when the discovery of an active parathyroid hormone by Collip[44, 45] made it possible to study hyperparathyroidism experimentally

Two years later Du Bois[7] and Aub[32] studied calcium and phosphorus metabolism of a patient with von Recklinghausen s disease of bone The metabolic changes resembled those following injection of parathormone A diagnosis of overactivity of the parathyroid glands was made, and in April 1926 the neck was explored with the idea of correcting the metabolic disorder by resection of parathyroid tissues Removal of two parathyroid glands failed to benefit the patient, and it was not until several years later that a tumor of an abnormally placed parathyroid gland was located and removed In the meantime Mandl, a surgeon of Vienna, operated upon a patient with the same type of bone disease and removed a parathyroid tumor The operation was followed by clinical improvement and partial correction of the bone defect Following this the study of similar cases by Gold by Barr and Bulger, who first used the name of hyperpara

characteristic but less constant are the fibrosing osteitis in which fibrous tissue replaces bone with formation of encapsulated fluid filled cysts and the collections of osteoblasts and osteoclasts which in the past have been known as benign giant cell tumors or osteoclastomes These form most often in the long bones but may involve the jaw (Fig 3) the pelvis the ribs or even the bones of the head The extent to which the osseous lesions may progress is well shown in the skeletons studied by von Recklinghausen[118] and by Schonenberger[129] Microscopically the swellings show hemorrhages which in some cases seem to dominate the picture There is extensive fibrosis in which a great number of giant cells may be found (Fig 4) Considerable difference in opinion exists as to the cause of the skeletal lesions of hyperparathyroidism one school believing that the decalcification of bone is due to a direct action of parathyroid hormone on bone[101] and the other holding that the changes in the skeleton are secondary to factors which cause loss of calcium from the body[18] Whatever may be the explanation there is an increased absorption of bone which causes weakening of osseous structures with hemorrhages and fractures It does not interfere with the processes of repair and injuries of bone are followed by intense osteoblastic activity as well as by increase in stroma of the bone marrow and fibrosis The concurrent osteoblastic and osteoclastic activity in the skeleton account for many of the variations in the clinical picture

In hyperparathyroidism secondary to nephritis extensive osseous lesions have been observed When the nephritis develops in childhood and when the bones are undergoing endochondral ossification a condition known as renal dwarfism may occur[11] Bones are decalcified and deformed and skeletal growth is retarded In some cases[111] there have been no demonstrable bone changes This is ostensibly due to an intake of calcium as with great milk drinking which is sufficiently high to keep up with the excessive output

Teeth — Cysts or tumors of the jaw may cause malocclusion or distortion of the normal arrangement of the teeth Considering the extensive changes which occur in osseous tissue it is remarkable that even in extreme cases of demineralization there is no increase in dental caries This seems to indicate that the resorption of calcium and phosphorus from mature teeth does not occur by way of the blood stream[125]

Metastatic Calcification — In several cases a remarkable deposit of calcium has been found in the soft tissues The alveolar walls of the lungs the glands of gastric mucosa and the convoluted tubules of the kidneys have been involved most often and it is probably significant that these are the places where acids are excreted from the body Metastatic calcification has not however been limited to these locations Dawson and Struthers[31] found calcium infiltration of practically every organ Pencke[114] in a case complicated with chronic nephritis found calcification in the left heart the smaller arteries the thyroid, the spleen and

not thoroughly understood There is, however, much evidence to support the idea that retention of phosphates is the probable cause, and it is significant that Drake[53] was able to produce parathyroid hyperplasia in rabbits by parenteral administration of phosphates Others however have suggested that low serum calcium[16] or a change in the calcium and inorganic phosphorus equilibrium is responsible[112] The etiology of secondary hyperparathyroidism recently has been well reviewed by Anderson[2]

The possibility of a combination of primary and secondary hyperparathyroidism exists when renal lesions consequent to primary hyperparathyroidism stimulate the glands to still greater activity Cases in which this situation has developed have been reported by Soffer and Cohn[134] and by Downs and Scott[5]

Pathology

Parathyroid Hyperplasia and Tumors — The pathology of the parathyroid glands has been studied extensively by Castleman and Mallory[39 40] and by Hunter and Turnbull[82] Adenomas usually weigh from 0 5 to 20 gm, but one weighing 101 gm has been reported[133] Most of them are composed predominantly of chief cells but in rare instances oxyphile cell tumors[141] have been described Malignant tumors as a cause of hyperparathyroidism are excessivly rare[6] In the case reported by Meyer Rose and Ragins[106] hyperparathyroidism polycystic disease and nephrolithiasis were dependent upon a carcinoma of the parathyroid, removal of which caused only temporary improvement with later recurrence and malignant metastases

In 162 cases of hyperparathyroidism reviewed by Castleman and Mallory 128 showed a localized growth in a single parathyroid gland, 12 showed localized growths in more than one gland while 22 showed diffuse hyperplasia of all glandular tissue In 2 of these the hyperplasia seemed to be of chief cells The remaining 20 presented a remarkable picture characterized by cells of enormous dimensions containing large amounts of clear lightly staining cytoplasm In such cases at the Massachusetts General Hospital the total amount of parathyroid tissue was 40 to 100 times normal and individual cells had a radius 5 times normal and volume 125 times normal suggesting that the process might represent hypertrophy rather than hyperplasia

The change in the glands in renal hyperparathyroidism appears to be a true hyperplasia affecting all glands but not to the same degree Enlargement may be great and a single gland may attain a size of 5 gm

Changes in the Bones — Decalcification of the skeleton is the most constant osseous manifestation This is attributable to the hyperparathyroidism It is not related directly to rickets or to osteomalacia although possibly in some cases the hyperparathyroidism has been complicated by these conditions More





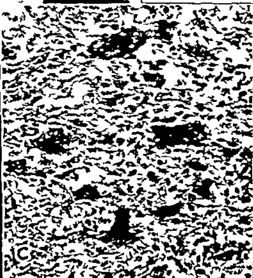


FIG 4 A X ray sho ι ng giant cell tumor of first phalanx of fore finger
B Long tudinal section through amputated finger showing gross appearance of the tumor
C Microscopical appearance of tumor showing fibrosis and giant cells.

skin as well as in the walls of a parathyroid tumor Most significant is the occurrence of metastatic calcification in the experimental condition produced by excessive dosage of parathormone In the hyperparathyroidism secondary to renal disease there may be most extensive calcification of the arteries[77], calcification of the skin[116] or calcification about joints[10]



Fig 3 Case of hyperparathyroidism (Barr and Bulger showing tumor of left maxilla abnormal mobility of joints and extreme flabbiness of muscles

Nephrolithiasis — Because of the increased urinary excretion of calcium and phosphate patients with hyperparathyroidism are predisposed to the formation of urinary calculi of calcium phosphate or of calcium oxalate Renal stones have been a feature in about 70 per cent of the cases Obstruction and infection secondary to *nephrolithiasis* are common and account for many of the deaths

tion[71] In one of the cases described by Barr and Bulger (Fig 3) the muscular weakness was combined with an abnormal mobility of joints

Genitourinary Symptoms — Complaints referable to the urinary tract may be the first to call attention to the disease Albright[18] has emphasized that these may be dependent upon three types of lesion (1) pyelonephritis secondary to the formation of calcium phosphate stones (2) nephrocalcinosis in which calcium deposits in renal parenchyma are predominant (3) acute parathyroid poisoning with calcium deposits in the kidneys as well as in other organs The symptoms associated with the formation and development of stones in the pelves or ureters are the same as those from nephrolithiasis of any origin Due to irritation or infection of the bladder frequency of urination may be an early symptom Polyuria may occur even in patients whose renal function otherwise appears to be normal It may be so marked as to suggest diabetes insipidus There may be intermittent attacks of pain Renal insufficiency may occur from hydronephrosis or from pyelonephritis in association with stones or from extensive renal calcinosis

Circulatory Symptoms — *Cardiac irregularities and conduction defects have* been noted[46] High blood pressure may or may not accompany the renal insufficiency of the disease[132, 137]

Hematological Manifestations — Because of extensive fibrosis of the bone marrow anemia and leucopenia have been encountered occasionally in hyperparathyroidism Increased viscosity of the blood which is seen when excessive amounts of parathormone are given experimentally is not often a feature of clinical cases

Gastrointestinal Symptoms — Many patients complain of constipation and flatulence and some have nausea with attacks of vomiting

Parathyroid Tumor — Occasionally a parathyroid tumor may be palpated in the region of the thyroid gland The chance of doing so is enhanced by asking *the patient to swallow while the neck is being felt More often no tumor is identi*fied even when the swelling is of considerable size The usual position of the parathyroid glands posterior to the thyroid makes palpation difficult Differentiation from thyroid adenoma cannot be made accurately Furthermore a number of tumors have arisen from one of the inferior glands which may lie beneath the clavicle or sternum while still others are in the anterior mediastinum lying upon or imbedded in the thymus gland

Hypercalcemia and Abnormalities in Calcium and Phosphorus Metabolism — Jacoby and Schroth[84] were the first to investigate the calcium metabolism in osteitis fibrosa cystica Mandl found an increased excretion of calcium in the urine, which was reduced to one sixth of the original amount following the removal of a parathyroid tumor[103] Subsequent studies by many observers have established an abnormally high excretion of calcium in the urine as a feature,

from the disease Calcium salts may be deposited also in the renal parenchyma as a form of nephrocalcinosis which leads to inflammatory changes, sclerosis and contracted kidneys Acute poisoning with parathormone may be associated with extensive calcium deposits in the kidney and other organs[11 12]

Clinical Features

Pain — The most prominent symptom in active hyperparathyroidism is pain This may be intensified by weight bearing It is referred by the patient to the bones and joints and may simulate the distress of early arthritis At other times it has been mistaken for a polyneuritis

Other Symptoms Referable to the Bones — Cysts or giant cell tumors may occur in any bone (Fig 4) but are most frequent in the femur and humeros They often appear at the site of an injury The pulling of a tooth may be followed by a progressive swelling of the jaw or a relatively slight blow may cause the development of a tumor on one of the long bones Although pains in the bones and muscles are not uncommon, the swellings themselves usually are painless When covered by heavy musculature as in the thigh, they may be entirely unsuspected, until a pathological fracture calls sudden attention to their presence

Stooping due to an increasing kyphosis and bowing of the legs may be noticed by the patient or his friends Sometimes there is a startling loss of height as in the patient described by Hannon, Shorr McClellan and Du Bois[73], who shrank more than four inches

X ray of the bones reveals localized cysts and tumors with marked thinning of the cortex (Fig 4) It also shows in most cases a somewhat irregular rare faction and in advanced cases an abnormal bending of weight bearing bones The femurs and to a less extent the tibiae may be involved Often there is irregular but gross deformity of the pelvis and kyphosis of the spine with rarefaction and thinning of the vertebral bodies That the decalcification is quite general is indicated by the bending of the terminal phalanx of the thumb which is much used for pressure in many occupations

Fractures are frequent and in advanced cases contribute greatly to the picture of bizarre deformities Although the decalcified bones are broken with great ease they offer no special difficulties in healing, the callus usually being of normal character

Muscular Weakness — In hyperparathyroidism there is diminished excitability of nerves and muscles a condition apparently the exact opposite to that of tetany The muscles may be moved but are unusually flabby Weakness is a constant complaint and may be so extreme as to cause semi invalidism or even to prevent walking The deep reflexes are not abolished and indeed in some patients are exaggerated Electrical tests show diminished response to stimula

tion[73] In one of the cases described by Barr and Bulger (Fig 3) the muscular weakness was combined with an abnormal mobility of joints

Genitourinary Symptoms — Complaints referable to the urinary tract may be the first to call attention to the disease Albright[18] has emphasized that these may be dependent upon three types of lesion (1) pyelonephritis secondary to the formation of calcium phosphate stones (2) nephrocalcinosis in which calcium deposits in renal parenchyma are predominant (3) acute parathyroid poisoning with calcium deposits in the kidneys as well as in other organs The symptoms associated with the formation and development of stones in the pelves or ureters are the same as those from nephrolithiasis of any origin Due to irritation or infection of the bladder frequency of urination may be an early symptom Polyuria may occur even in patients whose renal function otherwise appears to be normal It may be so marked as to suggest diabetes insipidus There may be intermittent attacks of pain Renal insufficiency may occur from hydronephrosis or from pyelonephritis in association with stones or from extensive renal calcinosis

Circulatory Symptoms — Cardiac irregularities and conduction defects have been noted[56] High blood pressure may or may not accompany the renal insufficiency of the disease[132, 137]

Hematological Manifestations — Because of extensive fibrosis of the bone marrow anemia and leucopenia have been encountered occasionally in hyperparathyroidism Increased viscosity of the blood which is seen when excessive amounts of parathormone are given experimentally is not often a feature of clinical cases

Gastrointestinal Symptoms — Many patients complain of constipation and flatulence and some have nausea with attacks of vomiting

Parathyroid Tumor — Occasionally a parathyroid tumor may be palpated in the region of the thyroid gland The chance of doing so is enhanced by asking the patient to swallow while the neck is being felt More often no tumor is identified even when the swelling is of considerable size The usual position of the parathyroid glands posterior to the thyroid makes palpation difficult Differentiation from thyroid adenoma cannot be made accurately Furthermore a number of tumors have arisen from one of the inferior glands which may lie beneath the clavicle or sternum while still others are in the anterior mediastinum lying upon or imbedded in the thymus gland

Hypercalcemia and Abnormalities in Calcium and Phosphorus Metabolism — Jacoby and Schroth[83] were the first to investigate the calcium metabolism in osteitis fibrosa cystica Mandl found an increased excretion of calcium in the urine which was reduced to one sixth of the original amount following the removal of a parathyroid tumor[103] Subsequent studies by many observers have established an abnormally high excretion of calcium in the urine as a feature

which is to be expected in all cases except those which have developed a complicating renal insufficiency[137, 52] The calcium content of the serum usually is increased In a review of 114 cases of hyperparathyroidism, in which the calcium concentration of serum was recorded, Gutman [2] found that 109 had over 11 mgm and 91 had over 12 mgm per 100 c c Albright and his associates[1], however reported a number of proven cases of hyperparathyroidism, in which the average concentration of the serum was below 12 mgm per 100 c c In a case observed by Snapper[130] calcium in the serum reached the quite astounding value of 23 6 mgm per 100 c c Inorganic phosphorus usually is diminished Of 79 cases in Gutman s series values of less than 2 5 mgm per 100 c c were recorded in 35 In some the serum phosphorus has a value of less than 1 5 mgm per 100 c c In cases with renal damage or on occasions when the calcium values are greater than 15 mgm per 100 c c the inorganic phosphorus may be normal or rise above normal levels During active stages of the disease alkaline phosphatase is increased above normal indicating perhaps a marked tendency to bone repair in a disease in which osteoclastic processes are predominant In one case a high level of acid phosphatase was recorded[56]

Diagnosis

In considering the diagnosis of hyperparathyroidism the experience of the group at the Massachusetts General Hospital is instructive Of 67 cases reported by Cope[48] 30 per cent were diagnosed because of osseous tumors and cysts 15 per cent because of decalcification of the skeleton and renal stones, while 55 per cent were recognized because of renal stones alone Obviously the condition must be suspected in all diseases of the skeleton and in all cases showing evidence of renal stones Other symptoms, which may suggest the diagnosis are weakness diminished tone and lessened excitability of muscles Tumors or cysts of the jaw or even malposition of teeth may call attention of the alert dentist to the possibility of the disease Confirmation usually will depend upon the demonstration of hypercalcemia or of abnormal excretion of calcium in the urine The Sulkowitch test and its modifications have proved useful in early diagnosis

Hypercalcemia is rare in conditions other than hyperparathyroidism An increase of serum calcium has been seen after the administration of large amounts of viosterol and has been shown by Brown and Roth[36] in patients suffering from polycythemia Although it has been reported in some cases of gout and arthritis most observers have failed to demonstrate it It may appear dissociated from parathyroid overactivity in conditions in which serum protein is greatly increased, and it is necessary as McLean and Hastings[107] have shown to take protein into account in evaluating serum calcium levels The presence of hypercalcemia always should suggest hyperparathyroidism and if the previously mentioned conditions can be excluded may be regarded as pathognomonic

The importance of early diagnosis has led to attempts at inclusion under the category of hyperparathyroidism many conditions which have no relation to it It is not surprising that confusion has arisen concerning the generalized demineralization of the skeleton which is encountered so frequently in post menopausal women in eunuchoidism in Cushing s syndrome and in old age It is now clear that these rarefactions of the skeleton are due primarily not to a process of decalcification but to a failure in the formation of the normal matrix of the bone in which calcium is deposited

From the standpoint of the roentgenologist there may be also some confusion of diagnosis with adult rickets or osteomalacia While the pictures in these conditions may be quite similar the mechanism is different in that the defect arises from a failure in depositing calcium rather than from an increased tendency to decalcification

A few years ago an attempt was made to show that Paget s disease (osteitis fibrosa) was a form of hyperparathyroidism Essential differences in pathology as well as the failure to demonstrate hypercalcemia or parathyroid hyperplasia in Paget s disease have served to exclude the possibility

Of great interest in the differential diagnosis are the cases collected and described by Albright[6, 21] and variously designated as Albright s disease osteitis fibrosa cystica disseminata fibrous dysplasia of bone and polyosteiotic fibrous dysplasia This condition is characterized by brown spots (cafe au lait spots) on the body soft tissue tumors (neurofibromata) occasional precocious puberty in females and involvement of any part of the skeleton often unilateral but never generalized An excellent review of this desease has been published recently by Thannhauser[137] who regards it as a form of neurofibromatosis an interpretation more recently questioned by Jaffe It is not associated with any demonstrable changes in calcium metabolism

In considering the differential diagnosis account must be taken also of conditions which produce secondary hyperparathyroidism Occasionally there may be difficulty in differentiating renal insufficiency which has arisen because of hyperparathyroidism from renal difficulty which is primary and has led to overactivity of the parathyroids

In the literature there are cases which have been diagnosed as renal calcinosis or renal rickets but which on review seem to be classified better as primary hyperparathyroidism Some confusion may arise also between osteitis fibrosa cystica and multiple myeloma or carcinomatous metastases to bone especially when such cases are accompanied by hyperplasia of the parathyroid glands by hypercalcemia hyperphosphatemia and generalized decalcification of the skeleton At times diagnosis must rest on the radiological appearance of the osseous lesions or upon the historical evidence that they have developed from a primary tumor

Treatment

Medical treatment in hyperparathyroidism is of little or no avail While demineralization and to some extent, the fibrocystic disease of bone may be prevented by the intake of large amounts of calcium and phosphorus, this treatment in itself predisposes to the even more serious nephrolithiasis and nephrocalcinosis Irradiation of the parathyroid glands in cases of tumor or hyperplasia has not been encouraging although individual cases have appeared to respond with temporary benefit

The treatment of choice is surgical, but there is general agreement that for the best results special experience in parathyroid surgery is desirable or at times essential[41 46 47 48] Even a surgeon of great experience may have difficulty in locating the glands or in correctly identifying a tumor The parathyroids may number as many as twelve, they may be scattered in the substance of the thyroid gland in the thymus or in the anterior or posterior mediastinum Furthermore, there may be considerable difficulty in differentiating parathyroid from thyroid tissue or even from globules of fat In some cases the tumor has been found only after two or more explorations For more complete examination in difficult cases Cope has devised a two stage operation in which the neck and posterior mediastinum are explored first with a later exploration of the anterior mediastinum and the region of the thymus gland

There is considerable danger of tetany following the removal of a tumor or of a large amount of hyperplastic tissue Symptoms may develop in a few hours and, unless promptly and thoroughly treated may be rapidly fatal The likelihood of such an occurrence to some extent is predictable by a study of the level of alkaline phosphatase which tends to be high in cases showing intense osteoblastic activity and hence a tendency to rapid withdrawal of calcium from the circulation Treatment with calcium gluconate parathormone and calciferol should be prompt and is conducted as in other cases of acute tetany as described earlier in this chapter

To avoid such emergencies probably it is wise to administer prophylactically 100 000 to 400 000 units of calciferol with 6 to 12 grams of calcium lactate or calcium gluconate each day from the day of operation until all danger of tetany is passed The use of the Sulkowitch test at frequent intervals is of much assistance in anticipating the onset of tetany and in judging safe dosage of calciferol and calcium Complete absence of a precipitate in the urine indicates a serum calcium of 8 mgm per 100 c c or lower and a heavy precipitate indicates undesirably high calcium levels

Results of surgical treatment often are brilliant However, a follow up of every patient for a number of years should be carried out routinely Examination of the urine by the Sulkowitch reagent should disclose undesirable levels of cal

cium in the serum X rays of the skeleton taken at three month intervals will reveal remineralization in favorable cases If the disease has been associated with nephrolithiasis or with renal calcinosis the removal of a tumor or hyperplastic tissue may do no more than prevent further deposits Renal insufficiency if apparent before operation may remain uncorrected Danger of secondary urinary tract infection is considerable Deaths from renal infection and failure in cases otherwise aided have not been infrequent

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CHAPTER XV-A

DISEASES OF THE THYROID GLAND

By Samuel L. Gargill and Mark Falcon Lesses

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PART I

ANATOMY BIOCHEMISTRY AND PHYSIOLOGY OF THE THYROID

ANATOMY

In man the thyroid gland originates during the third week of embryonic life as an invagination of the pharyngeal entoderm anterior to the tracheal invagination In later life the site of its origin is the foramen cecum located at the base of the tongue At first a hollow tube the thyroid anlage becomes a solid mass of cells which later descend through the thyroglossal tract into the anterior portion of the neck forming epithelial bands and fenestrated plates The primary thyroid follicles arise directly from these epithelial plates The thyroglossal tract usually disappears early in embryonic life Thus embryologically the thyroid gland is a detached clump of entodermal tubules in front of the trachea [1]

The human thyroid attains full size just before puberty The gland normally comprises two lateral lobes connected by an isthmus An additional lobe known as the pyramidal lobe may be present especially in areas of endemic goiter This lobe arises from epithelial rests along the thyroglossal tract and is recognizable as a strip of tissue reaching from the isthmus toward the hyoid bone on the left side of the thyroid cartilage The adult thyroid normally weighs between 20 and 25 gm averaging 0 4 gm per kilo of body weight it is larger in women than in men The whole gland is firmly attached to the trachea and therefore moves with that organ in swallowing

The blood supply of the thyroid gland is of such magnitude that it clears the total blood volume of a normal man in about one hour The blood is delivered to the gland through the four thyroid arteries the right and left superior and inferior arteries The superior descend from the external carotid artery to the upper poles of the thyroid The inferior arise from the subclavian arteries to reach the posterior surface of the lower poles Occasionally the median thyroidea ima artery is encountered ascending from the innominate artery in front of the trachea to

into the deep cervical retrosternal tracheal and anterior laryngeal lymph nodes

Both sympathetic and parasympathetic fibers innervate the thyroid gland The sympathetic fibers are derived from the second to the fifth thoracic segments passing through the superior and middle cervical ganglia, whence they are relayed to the gland through the superior laryngeal nerve and along blood vessels The parasympathetic fibers are derived from the vagus and enter the thyroid by way of the superior laryngeal nerve The exact role of the rich innervation of the thyroid is as yet undetermined, it is clear that there is a complex and sensitive vasomotor control but it is uncertain whether nervous control of hormonal secretion exists



Fig 2 Cross section of normal human thyroid Cross section of the superior anterior region of the dissected left lobe shown in Fig 1 demonstrates anastomosing channels or spaces forming a fenestrated labyrinth It is to be noted that clefts do not completely traverse the gland From Rienhoff W F Jr Arch Surg 1929 xix 986 1036

The parenchyma of the thyroid has been shown by Rienhoff to be a complex mass of tissue irregularly subdivided into many areas These areas of tissue consist of groups of follicles of varying number size and shape The parenchyma itself is unevenly compartmented by connective tissue septa which convey the blood vessels nerves and lymphatics (Figs 1 and 2)

the lower portion of the thyroid gland These larger arteries divide and ramify over the surface of the gland, whence penetrating vessels enter deeply into the thyroid structure forming a capillary bed around each follicle

The venous drainage starts from the perifollicular plexus and empties into the internal jugular veins by way of the superior and middle thyroid veins and into the innominate veins by way of the inferior thyroid veins Lymphatic drainage is provided by a perifollicular plexus which empties

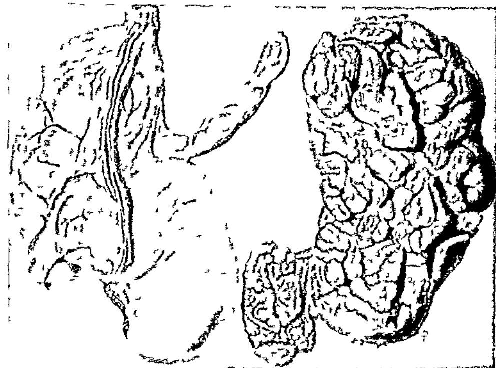


Fig 1 Normal human thyroid right and left lobes together with the isthmus The dotted line shows where the isthmus which in the section was left attached to the left lobe joins the base of the right lobe The right lobe is shown covered with fascia as it was found in the cadaver The anterior branch of the superior thyroid vessels is seen descending from the upper toward the lower pole From the junction of the upper portion of the right lobe can be seen a bizarre pyramidal lobe The isthmus and the left lobe are shown with all fibrous tissue investment including blood vessels nerves and lymphatics dissected away It is to be noted that there are no true lobules but a complex mass of parenchyma irregularly divided by an intricate anastomosing system of spaces or channels forming within the gland a veritable fenestrated labyrinth The gland as shown is made up of regions of connecting bars bands or plate like regions composed of individual discrete follicles or acini The stippled appearance of the surface represents the follicles From Rienhoff W F Jr Arch Surg 1929 xix 986 1036

into the deep cervical retrosternal tracheal and anterior laryngeal lymph nodes

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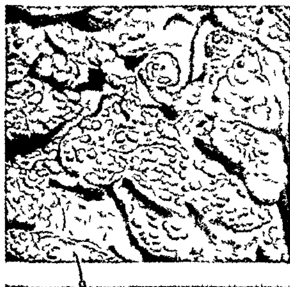


Fig 2 Cross section of normal human thyroid Cross-section of the superior anterior region of the dissected left lobe shown in Fig 1 demonstrates anastomosing channels or spaces forming a fenestrated labyrinth It is to be noted that clefts do not completely traverse the gland From Rienhoff W F Jr Arch Surg 1929 xix 986 1036

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The follicle is the structural and functional unit of the thyroid It is a cyst-like structure varying in size from 50 to 1000 mu with an average measurement of about 300 mu A single layer of simple epithelial cells, low columnar or cuboidal comprise the wall of the follicle, within which there is a varying amount of a hyaline uniform material called colloid' The follicles vary in shape from a sphere to a cube, thus many are rounded while others are angular Each follicle is an isolated unit, and evidence is lacking for any intercommunication (Fig 3)

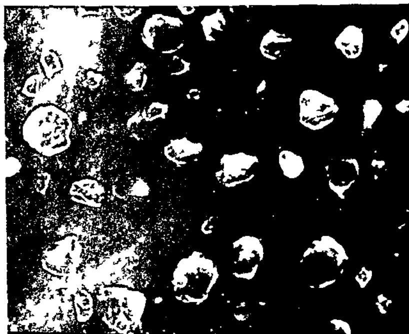


Fig 3 Group of follicles dissected from normal human thyroid Spherical shape together with the variability and thickness of the epithelial mass as evidenced by the difference in the photographic shadow cast is well brought out From Rienhoff W F, Jr Arch Surg 19 9 xix 986 1036

The thyroid cell is a complex structure containing a large rounded reticular nucleus and cytoplasm in which special stains have demonstrated mitochondria and the Golgi apparatus The former are granules or filaments whose structure parallels quantitatively the secretory activity of the gland[3 4] The Golgi apparatus is a coarse thread like structure of the cytoplasm which occurs in the thyroid gland as well as in other secretory glands such as the pancreas and ovaries Its form and position vary with the activity of the cell and eventually it becomes fragmented

Cramer and Ludford[3] have advanced the interesting theory that the mitochondrial granules serve to increase or decrease the intracellular surfaces in accordance with secretory requirements Ingram[5] showed that the size of the Golgi apparatus is proportional to the size and secretory content of the follicular cells The height of the cell itself is a useful index of thyroid function for the cell elongates with increased activity and becomes flattened with rest[6]

The manner in which the thyroid cell secretes its hormonal produce has been demonstrated by Williams[7] who observed living thyroid follicles implanted in the ear of the rabbit The follicles underwent cyclic changes in activity divisible into these four stages (1) secretion characterized by an increasing refractility of the thickened walls and by the roundness of both follicle and colloid (2) secretion and colloid release characterized by further increase in refractility of the walls with diminution in their thickness increase in colloid and in active follicles by irregularity of the internal border of the wall the irregularity being explained tentatively as due partly to compression of exhausted cells to such a degree that diffusion of colloid across them can take place this appears to be the chief mechanism of colloid release (3) partial collapse caused by colloid release at greater velocity than colloid production (4) recuperation characterized by an opacity of the walls which are thickened and enclose very little colloid Williams concluded that secretion is toward and into the lumen by diffusion

The nervous innervation of the follicle appeared to play no part in secretion under the conditions of his experiment On the other hand anterior pituitary extracts containing the thyrotrophic hormone augmented colloid production and release

The mechanism of release of follicular colloid in man has been considerably elucidated in studies on necturus by Grant[8] who demonstrated that stored colloid emptied into the blood capillaries surrounding the follicles under the influence of anterior pituitary implantation As a consequence of her experiments she has advanced a theory of transcellular colloid release During the transfer stage the colloid in the follicle cells is seen first as large refractile droplets which later appear fine and emulsified Since the follicles showed progressive emptying the colloid content of the cells must be regarded as proof of transcellular colloid release rather than as a product of synthesis The mechanism by which the colloid crosses the cell boundary is unknown though emulsification enzymatic digestion and phagocytosis have been variously advanced as possible explanations In the mammalian gland the follicular cells per

haps transport the colloid through their cytoplasm in an unstainable form, in necturus one can obtain histological proof of this method of colloid export

Gersh and Caspersson,[9] through studies of frozen-dried thyroid gland sections with the ultraviolet microscope, have contributed significantly to the understanding of colloid release Thyroglobulin has a characteristic absorption curve in the ultraviolet region of the spectrum, with absorption characteristics allowing separation of tyrosine and tryptophane on the one hand and thyroxine and diiodotyrosine on the other Application of this knowledge through methods developed by Caspersson allowed the quantitative concentration of total protein in the colloid and of thyroxine and diiodotyrosine in both colloid and cells to be determined The protein-bound iodine comprising thyroxine and diiodotyrosine, was found homogeneously distributed in the colloid The administration of potassium iodide or anterior pituitary extract produced continual secretion of colloid into the lumen for storage and subsequent reabsorption Markedly stimulated glands showed secretion directly toward the blood vessels

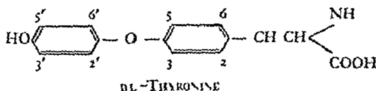
Dempsey[10] has also investigated the histochemistry of the thyroid through a study of its fluorescent qualities Intrafollicular colloid the follicular cells connective tissue and thyroid pigment revealed autofluorescence when viewed through an ordinary microscope illuminated with ultraviolet rays Deficient fluorescence of the colloid occurred in iodine and hormone-deficient glands Further studies of the chemical cytology of the thyroid by Dempsey and Singer[11] have provided evidence that the colloid contains a conjugated protein ribonucleoprotein, in addition to the simple protein thyroglobulin The significance of this finding in relation to thyroid physiology is at present unclear These authors and others have found both alkaline and acid phosphatases in the thyroid gland apparently participating in its intermediary carbohydrate metabolism The phosphatases are deposited in varying concentration in some of the endothelial cells of the capillaries thus suggesting a mechanism for controlling migration of metabolites through the capillary wall (Plates 1 and 2)

Biochemistry

The epithelial cells of the follicle secrete the colloid substance, which is stored within the lumen The thyroid hormone is ordinarily contained

in this material and thus it represents a unique example of an internal secretion that can be visualized with the microscope Thyroglobulin can be extracted from the gland with physiological salt solution and by appropriate precipitation with varying concentrations of ammonium sulfate its proteins may be salted out [12] Bauman [13] in 1896 first showed that the thyroid protein contained iodine and that the iodine in the gland was organically bound Hutchison [14 15] recognized that the protein was globulin and later investigation has demonstrated that except for its iodine content this iodo thyroglobulin does not differ markedly from other globulins of animal origin [16] The molecular weight of thyroglobulin has been determined to be about 675 000 [17]

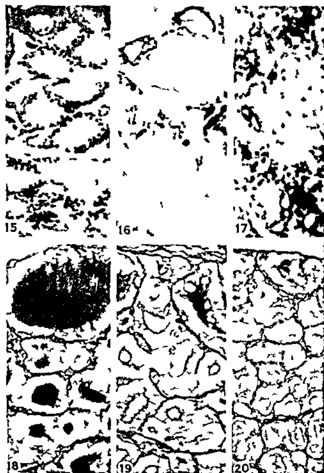
The iodine of the thyroid is derived immediately from the circulating blood and ultimately from the iodides and iodates of ingested food and water Iodates are converted to iodides in the intestinal tract and are absorbed in the latter form By means of radioactive iodine [18] it has been established that the thyroid of the normal rabbit is saturated with the halogen within 15 minutes after an intravenous iodine injection The iodine thus acquired is organically bound for hormone synthesis or rediffuses into the blood stream The normal thyroid gland does however contain 7 per cent of its total iodine in inorganic form



DL-THYRONINE

The physiological potency of thyroglobulin depends chiefly upon its content of two iodine-containing amino acids namely thyroxine and diiodotyrosine the former probably accounting for 29 per cent and the latter for 64 per cent of the total iodine in the normal gland Thyroxine containing 65 per cent iodine was isolated by Kendall in 1915 [19] Harington [20] proved that thyroxine is an amino acid with four iodine atoms a hydroxyphenyl ether of tyrosine or 3 5 3 5 tetra iodothyronine Harington and Barger [21] later synthesized thyroxine by conjugating two molecules of diiodotyrosine

Plate I



15. Fructose diphosphatase reaction, pH 9.5, in the endothelial and follicular cells of the thyroid gland from a normal control rat. The section was incubated for 24 hours in the substrate mixture, and the precipitated phosphate was visualized by transformation to cobaltous sulfide. Fixation in cold 80 per cent alcohol.

16. Thyroid gland from a rat exposed to cold, illustrating the reduction in the alkaline fructose diphosphatase reaction. The enzyme does not appear in the endothelium or parenchymal cells associated with the central or most active follicles, but is restricted to the peripheral inactive portions of the gland. Fixation in cold 80 per cent alcohol.

17. Alkaline fructose diphosphatase in the thyroid gland of a rat to which thiouracil had been administered. Fixation in cold 80 per cent alcohol.

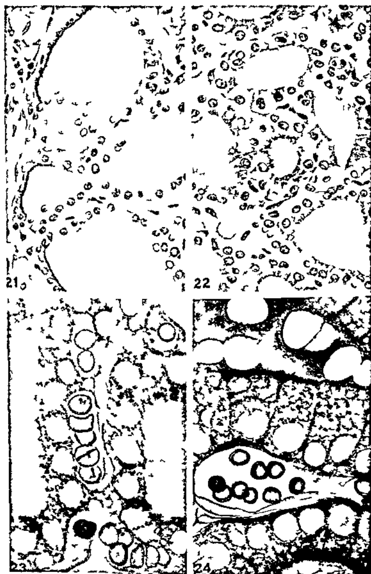
18. Argyrophilia of the colloid from the thyroid gland of a normal control rat. Bouin fixation, section digested in saliva. Pap's stain.

19. Section illustrating the reduction in argyrophilia, particularly in the central follicles, from a rat exposed to cold. Bouin fixation, section digested in saliva. Pap's stain.

20. Section illustrating the further reduction in argyrophilia in the thyroid gland of a rat to which thiouracil had been administered. Bouin fixation. Sections digested in saliva, Pap's stain.

From Dempsey, W. W. and Singer, M. Endocrinology, 1946, xxxviii, 270-95.

Plate 2



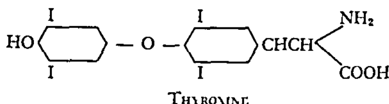
21 Drawing illustrating the localization of alkaline glycerophosphatase (pH 9.4) in the follicular cells of peripheral follicles from the thyroid gland of a normal control rat The endothelial cells are negative Fixation in cold 80 per cent alcohol Section incubated in substrate mixture for 6 hours

22 Drawing illustrating the localization of acid glycerophosphatase in the nuclei and parenchymal cells of the central follicles from the thyroid gland of a rat exposed to cold Fixation in 80 per cent alcohol Section incubated 48 hours

23 Drawing illustrating the argyophilic granules of the follicular epithelium of a normal control rat This appearance has been observed only after Zenker fixation

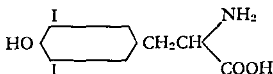
24 Argyrophilic granules in the thyroid gland from a rat after exposure to cold Zenker Fixation Pap s stain

From Dempsey W W and Singer M Endocrinology 1946 xxxviii 270–95



THYROXINE

This compound has been isolated in pure form from the gland by Oswald in 1911 and from the colloid by Harington and Randall in 1929 [3] Diiodotyrosine has the following structural formula



The biosynthesis of thyroxine appears to involve two stages first the iodination of tyrosine second the coupling of two molecules of diiodotyrosine to form thyroxine The derivation of diiodotyrosine from the essential amino acid tyrosine has been established by various methods It probably involves oxidative processes capable of liberating iodine from iodide to make it available for attachment to the tyrosine molecule Gavett [4] analyzed various thyroglobulins with regard to their amino acid content and found the tyrosine content to vary inversely with the content of thyroxine and diiodotyrosine He also showed that thyroglobulins low in iodine had a greater content of tyrosine and conversely that thyroglobulin from the glands of patients treated with iodine had more diiodotyrosine and thyroxine and less tyrosine This ability of the thyroglobulin molecule to alter its composition of amino acids explains the mechanism whereby iodine content and physiological potency of thyroglobulin may be varied

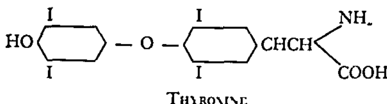
Further proof that iodination of tyrosine is the first step in the synthesis of thyroxine has been furnished through the use of radioactive iodine as a tracer substance This has been utilized by injecting radioiodine into animals and determining the subsequent distribution of radioactivity in the body or by studying the respiration of thyroid tissue slices in a medium to which radioactive iodine had been added and whose fate could be traced Following the injection of radio-iodine into animals there is rapid concentration of iodine in the thyroid gland [6, 7] This occurs quickly within a matter of minutes, and proceeds until as

much as 50 per cent of the radioactive material is found in the thyroid gland after 48 hours With tracer doses Morton and his co workers[29] have repeatedly shown that almost all of the radio iodine deposited in the gland is organically bound within one hour The radioactive iodine is distributed among three fractions inorganic iodide diiodotyrosine and thyroxine With passage of time there is gradual increase in the amounts of diiodotyrosine and thyroxine and decreasing amounts of inorganic iodide This work combined with the studies of Cavett mentioned above shows clearly the reciprocal relationship existing among tyrosine inorganic iodide diiodotyrosine and thyroxine

When large amounts of radioactive iodine are added to the medium in which surviving thyroid tissue slices are respiring there is rapid incorporation of the radio iodine in the tissue As in the in vivo experiments the radioactivity is associated at first with diiodotyrosine and later appears with thyroxine thus indicating a process of conversion similar to that seen in the intact animal[8, 31] It is of interest however that Schachner Franklin and Chaikoff[31] demonstrated that surviving thyroid slices were able to concentrate up to 60 per cent of added radio iodine even after the inhibition of thyroxine and diiodotyrosine formation by azide or sulfanilamide Cyanide and sulfide in addition to inhibiting thyroxine and diiodotyrosine formation also blocked the accumulation of radio iodine by thyroid slices From this selective blocking of iodine concentration and thyroxine formation these authors concluded that thyroid tissue possesses an additional mechanism for concentrating iodine that does not depend upon conversion of inorganic iodide to thyroxine and diiodotyrosine

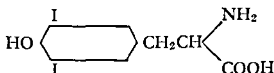
The role of tyrosine in the synthesis of thyroxine and as a scaffold for the attachment of iodine to the protein molecule may be best appreciated by Harington s statement[12] that it is possible by choosing the proper conditions almost to titrate the tyrosine in a protein with iodine While thyroxine and diiodotyrosine are the major iodine containing compounds of the thyroid chromatography has demonstrated that others are present particularly monoiodotyrosine[4, 38] in amounts up to 15 per cent of the total iodine

Iodination of tyrosine is the first step in hormone synthesis The coupling of diiodotyrosine to form thyroxine as the final step in the process must be considered in relation to certain enzyme systems that are involved in intracellular respiration Oxidation within the cell requires enzymatic action because the usual metabolites of the body are not auto oxidizable There are cellular iron containing pigments known as cyto



THYROXINE

This compound has been isolated in pure form from the gland by Oswald in 1911 and from the colloid by Harington and Randall in 1929.[3] Diiodotyrosine has the following structural formula:



The biosynthesis of thyroxine appears to involve two stages: first, the iodination of tyrosine; second, the coupling of two molecules of diiodotyrosine to form thyroxine. The derivation of diiodotyrosine from the essential amino acid tyrosine has been established by various methods. It probably involves oxidative processes capable of liberating iodine from iodide to make it available for attachment to the tyrosine molecule. Cavett[4] analyzed various thyroglobulins with regard to their amino acid content and found the tyrosine content to vary inversely with the content of thyroxine and diiodotyrosine. He also showed that thyroglobulins low in iodine had a greater content of tyrosine and, conversely, that thyroglobulin from the glands of patients treated with iodine had more diiodotyrosine and thyroxine and less tyrosine. This ability of the thyroglobulin molecule to alter its composition of amino acids explains the mechanism whereby iodine content and physiological potency of thyroglobulin may be varied.

Further proof that iodination of tyrosine is the first step in the synthesis of thyroxine has been furnished through the use of radioactive iodine as a tracer substance. This has been utilized by injecting radioiodine into animals and determining the subsequent distribution of radioactivity in the body, or by studying the respiration of thyroid tissue slices in a medium to which radioactive iodine had been added and whose fate could be traced. Following the injection of radio-iodine into animals there is rapid concentration of iodine in the thyroid gland.[5] This occurs quickly, within a matter of minutes, and proceeds until as

cytochrome C cytochrome oxidase system using an enzyme preparation from the rat heart

Thyroglobulin thus appears as a complex protein which incorporates three iodine containing amino acids in its molecule through iodination of tyrosine The iodine content of the normal human thyroid varies from 0 05 to 0 45 per cent of the dry gland[43] or from 0 5 to 4 5 mg per gram of dried thyroid The average iodine content of dried glands throughout the world is close to 0 2 per cent[44] (2 mg per gram dried gland) The iodine content varies depending upon the activity of the gland season of the year geography and food habits[45 46 47]

While the thyroid gland selectively fixes about 20 per cent of the body s iodine organically bound iodine is present in other tissues and thyroxine like fractions have been biologically demonstrated in these tissues The role of this extrathyroidal organic iodine is not clear but is undoubtedly significant

Chapman[48] found that the level of iodine intake had a pronounced effect on the weight surface area metabolic rate and food utilization of thyroidectomized animals those with higher iodine ingestion showing an effect which suggested that iodine might play a role in production of a thyroxine like substance in the tissues This aspect of extrathyroidal hormone production was more definitely established by Morton Chaikoff and their collaborators[44] through the use of radioactive iodine From 2 to 8 months following thyroidectomy radio-iodine was injected into young rats who were then killed at intervals of 2 to 96 hours after the injection Measurable quantities of labeled thyroxine and duodotyrosine were found in the liver muscles and small intestines The completeness of the thyroidectomy was checked both by serial section and by the radio autographic technique

These experiments indicate that tissues other than the thyroid possess the ability to elaborate small amounts of a thyroid like substance Harington[39] explains the extrathyroidal synthesis of thyroxine as a general biological function of almost any living tissue containing adequate amounts of iodide since tissue proteins will contain tyrosine bound in a peptide linkage whence it can undergo the reactions leading to thyroxine This would leave the thyroid gland the specific functions of concentrating iodine in large amounts of increasing the rate of formation of thyroxine and of storage of iodine containing amino acids in the form of thyroglobulin The possibility of this extrathyroidal synthesis of thyroxine is not surprising in view of studies on artificial iodo-proteins. Oswald [2] isolated crystalline duodotyrosine from hydrolysates of iodi

chrome a, b, and c, which are widely distributed in aerobic cells of many kinds and are especially abundant in tissues with large oxygen consumption. Oxidation of these pigments by molecular oxygen is accomplished by a respiratory enzyme known as cytochrome-oxidase. This enzyme which is readily inhibited by cyanide, is especially important in the oxidation of cytochrome a and c, less so for b, which is to some extent self-oxidizing.[35] With the aid of radio iodine Schachner, Franklin, and Chaikoff[36] have demonstrated that the formation of both diiodotyrosine and thyroxine in the thyroid is accomplished through intracellular aerobic oxidations involving the cytochrome-oxidase system. The need for cellular organization was indicated by the fact that homogenized thyroid tissue had lost its capacity to incorporate radio iodine. This incorporation does not occur with complete anerobiosis. Furthermore, typical inhibitors of cytochrome-oxidase, such as cyanide, azide, sulfide, or carbon monoxide, block the formation of diiodotyrosine and thyroxine from inorganic iodide in thyroid slices. Dempsey[10] has found cytochrome-oxidase in the cells of the thyroid follicle and has also presented evidence for the presence of peroxidase in the thyroid cells. The peroxidase reaction was easily inhibited by thiouracil, whereas the cytochrome-oxidase reaction was unaffected. DeRobertis and Grasso[37] have confirmed these findings.

Harington[38, 39] has postulated that the enzymic oxidizing system liberates iodine from iodides and that this free iodine is the effective oxidizing agent which converts both tyrosine to monoiodotyrosine and diiodotyrosine and the latter to thyroxine. According to Harington[39] diiodotyrosine or its derivatives in alkaline solution speedily liberate small amounts of iodine so that it is readily available as an oxidizing agent. Mild reducing agents that react with iodine, such as thiosulfate and many antithyroid drugs, inhibit this reaction. Further support to this view has been lent by Keston[40] who found that iodine and oxidases participate in the reaction which organically binds iodine. Recently Reineke and Turner[41] after a study of the factors influencing the iodination of casein, concluded that manganese had an important catalytic role in the promotion in vivo of thyroxine formation. Ray and Deysach[42] had earlier shown the particular ability of the thyroid to store manganese.

Thyroxine itself has an important role in enzymatic mechanisms. Gemmill[43] demonstrated that thyroxine increases the rate of oxidation of the ascorbic acid-ascorbic acid oxidase system (plant origin) and inhibits the cupric ion catalyzed oxidation of ascorbic acid. Thyroxine was also found to stimulate the oxidation of succinate in the dehydrogenase-

Harington has demonstrated that naturally occurring thyroxine is 3 5 3 5′ tetraiodo L thyronine The non halogenated amino acid DL-thyronine which resembles thyroxine structurally lacks thyroxine like activity The addition of iodine in the 3 and 5 positions to thyronine produces some thyromimetic action at a level of 1/15 to 1/40 of that of DL thyroxine If other halogens namely chlorine bromine and fluorine are added to thyronine thyroxine like activity develops but none is so potent as iodine Harington has concluded that thyromimetic activity develops only when the halogen atoms are present in the 3 and 5 positions of the thyronine nucleus Lerman Harington and Means [58] have found that the substitution of bromine or chlorine for iodine diminishes considerably the activity of the thyroxine molecule Tetrabromthyronine has 3 per cent and tetrachlorthyronine has 0 . per cent of the activity of L thyroxine

Naturally occurring thyroxine is levorotatory Commercially available *thyroxine has usually been racemic (that is* DL *thyroxine)* because it has been easier to isolate and synthesize in this form L thyroxine however, is now commercially available and has been found by us to be effective in the trea ment of myxedema The L isomer is much more potent than D thyroxine according to Gaddum Reineke and Turner consider the activity of DL thyroxine to be due entirely to the presence of the L isomer

These biological mechanisms for incorporating iodine into the body chemistry present the unsolved question of why the organism has selected iodine from among the elements to aid in the formation of an important cellular stimulant The intimate relation of iodine to the sea suggests an ancient paleochemical origin of the hormone Chlorine another halogen had already been utilized to form an essential component of the marine environment of our ancestors as well as an abundant component of human blood The question cannot of course be answered but serves to focus attention on the chemical genealogy of the hormone

The Nature of the Circulating Hormone

While the nature of the circulating hormone is at present unclear it is established that it lies somewhere between the large moleculed protein thyroglobulin and the relatively simple iodine containing amino acid thyroxine if in fact it is not either thyroglobulin or thyroxine Thyroglobulin which appears to be the form in which the hormone is present

nated albumin casein and gliadin Ludwig and von Mutzenbecher [0] iodinated casein and other proteins, thus producing products whose physiological activity was shown to be due to contained thyroxine and from which thyroxine was actually isolated Harington and Pitt Rivers have confirmed this work [1] These artificial iodo proteins and various fractions of their hydrolysates have physiological effects similar to those of the thyroid hormone [3] The iodinated proteins are of more than theoretical interest as a source of thyroxine-containing protein Reineke and Turner [54] have successfully produced synthetic thyro proteins which have several times the thyroidal activity of U S P thyroid powder, as judged by assay on tadpoles or by yield of thyroxine This increased activity appears entirely explicable on the basis of a content of thyroxine more than three times that normally obtained in powders derived from the dried gland Of considerable interest in connection with this finding is the further fact that the iodination of protein yields maximal thyroidal activity with substitution of two atoms of iodine per molecule of tyrosine An increase in iodination beyond this yields products of lesser activity Co operative studies in England have shown that iodinated casein as well as other iodinated proteins serve as an adequate stimulant of milk yield in the cow in a manner exactly similar to dried thyroid gland and thyroxine Such proteins also maintain growth in young thyroidectomized rats and effect premature metamorphosis in tadpoles

Only two mechanisms are available to explain the formation of thyroxine which has been proved to follow the iodination of proteins (1) either the protein contained thyronine (this is thyroxine less all four of its iodine atoms) which directly added iodine to form thyroxine or (2) the iodine produced diiodotyrosine from tyrosine and was then converted into thyroxine The latter process is perhaps the more likely and has been demonstrated by von Mutzenbecher to occur in minimal amounts as mentioned previously Thus the synthesis of thyroid hormone in the body and the iodination of protein in the test tube appear to follow a similar chemical pattern

The chemical structure of thyroxine has been shown to be specific by Harington and McCartney [56] who found a chemical isomer of thyroxine lacking the thyronine configuration to be inert This has been confirmed and extended by other workers, who have shown 'that a high specificity of structure is required to produce significant activity Substitution of the iodine atoms in unusual places (e g at positions 4', 6') strikingly reduced activity [7] Niemann [8] has exhaustively reviewed the chemistry of thyroxine and related compounds

Harington [6] has demonstrated that naturally occurring thyroxine is 3 5 3 5′ tetraiodo L thyronine The non halogenated amino acid DL-thyronine which resembles thyroxine structurally lacks thyroxine like activity The addition of iodine in the 3 and 5 positions to thyronine produces some thyromimetic action at a level of 1/15 to 1/40 of that of DL thyroxine If other halogens namely chlorine bromine and fluorine are added to thyronine thyroxine like activity develops but none is so potent as iodine Harington has concluded that thyromimetic activity develops only when the halogen atoms are present in the 3 and 5 positions of the thyronine nucleus Lerman Harington and Means [56] have found that the substitution of bromine or chlorine for iodine diminishes considerably the activity of the thyroxine molecule Tetrabromthyronine has 3 per cent and tetrachlorthyronine has 0 per cent of the activity of L thyroxine

Naturally occurring thyroxine is levorotatory Commercially available thyroxine has usually been racemic (that is DL thyroxine) because it has been easier to isolate and synthesize in this form L thyroxine however is now commercially available and has been found by us to be effective in the trea ment of myxedema The L isomer is much more potent than D-thyroxine according to Gaddum [9] Reineke and Turner [6] consider the activity of DL thyroxine to be due entirely to the presence of the L isomer

These biological mechanisms for incorporating iodine into the body chemistry present the unsolved question of why the organism has selected iodine from among the elements to aid in the formation of an important cellular stimulant The intimate relation of iodine to the sea suggests an ancient paleochemical origin of the hormone Chlorine another halogen had already been utilized to form an essential component of the marine environment of our ancestors as well as an abundant component of human blood The question cannot of course be answered but serves to focus attention on the chemical genealogy of the hormone

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in the gland itself, has not been found as such in the circulating blood except in the thyroid veins during or immediately after thyroidectomy for toxic goiter. Since Hektoen and his co-workers[61, 62] demonstrated that highly sensitive precipitin reactions to thyroglobulin could be developed through the use of immune serum the problem has been approached immunologically. This earlier work was extended by Lerman[63] who was unable to demonstrate thyroglobulin in the serum of thyrotoxic or normal persons. More direct evidence excluding thyroglobulin itself as the circulating hormone has been offered by Bassett, Coons, and Salter,[64] who found the major part of the circulating iodine in the albumin fraction, albeit the highest concentration of iodine was in the alpha and beta globulins.

Harington[65] has presented immunological experiments which support his view that thyroxine is the effective form of the circulating hormone. He immunized animals with artificial thyroxine-protein complexes, whose antigenic specificity was determined by thyroxine and diiodotyrosine groups. The antibodies of the antiserum thus produced were specifically adapted to combine with the molecule of the physiologically active substance and thus were able to interfere with the action of this substance in another animal by a process analogous with passive immunization. The antisera thus developed against the thyroxine protein complexes did not lower the metabolic rate of normal animals but did prevent the characteristic rise in metabolic rate caused by thyroglobulin or thyroxine. This neutralization of the effect of thyroxine by the antisera showed that the circulating antibodies containing combining sites adapted to thyroxine interfered with the access of the latter to its normal sites of action in the tissues.

Harington's hypothesis is only weakened by the work of Canzanelli and Rapport[66, 67] who found significant metabolic effects produced by thyroglobulin upon tissues in vitro and an absence of such effects by thyroxine. Barker,[68] as well as Williams-Ashman,[69] however, have found no in vitro effectiveness of thyroglobulin.

Craig and Salter[70] found that thyroxine when added to normal blood did not induce the calorigenic action in excised surviving tissues that was readily produced by the blood of thyroxinized animals, thus suggesting that thyroxine is altered in some way before becoming the effective form of the hormone. Thyroxine however has been found a complete metabolic substitute for the functioning thyroid gland in the living organism.

Gross and his associates[70] found that thyroxine, after its release by the thyroid gland circulates in combination with plasma proteins. This

combination may be readily separated by butanol but is reconstituted when thyroxine is placed in contact with plasma proteins. In further attempts to identify iodine compounds other than thyroxine and iodide in human plasma, Gross and Pitt-Rivers[96b, 96c] succeeded in demonstrating the presence of an iodine-containing substance in the plasma of patients given radioactive iodine which behaved in a manner identical with that of 3,5,3′-L-triiodothyronine on two-dimensional paper chromatograms and on a kieselguhr column. They concluded that this substance, triiodothyronine, is a normal constituent of the organic iodide fraction of plasma since they found it in the plasmas of *both euthyroid and hyperthyroid individuals. The steps in the biological* synthesis of thyroid hormone they formulated as follows: (1) oxidation of iodide to iodine; (2) iodination of tyrosine to diiodotyrosine; (3) coupling of 2 molecules of diiodotyrosine to give 1 molecule of thyroxine; and (4) deiodination of thyroxine to give triiodothyronine.

Triiodothyronine was then assayed in thiouracil-treated rats by its effect in preventing goiter.[96d] The activity of triiodothyronine was found to be about three times that of L-thyroxine, and it was concluded *that triiodothyronine is probably the form of the thyroid hormone that* is active in the tissues. Its effect in myxedema was then studied[107a] by administering it to two hypothyroid patients in a daily dose of 80 *micrograms. This dose had an effect similar to that of a daily oral dose* of 100 to 300 micrograms of L-thyroxine; the basal metabolic rate and blood cholesterol levels returned to normal and at the same time the patients lost weight during the treatment.

The metabolic effects of triiodothyronine as well as the metabolism and distribution of radioactive triiodothyronine have been further studied. Asper and his co-workers[108] observed that triiodothyronine produced an immediate metabolic effect five to ten times that of *equivalent doses of L-thyroxine in patients with myxedema.* Within six hours after its administration in a single subcutaneous dose (0.5 to 1.0 mg.) progressive increases in pulse rate and body temperature occurred, reaching a maximum on the third day. The basal metabolic rate increased promptly and there was acceleration of urinary creatine excretion as well as nitrogen and phosphorus diuresis with resultant negative nitrogen and phosphorus balances and weight loss. The serum protein-bound iodine levels increased after administration of triiodo*thyronine although they frequently remained in the hypothyroid range* when the patients were metabolically euthyroid. L-thyroxine, on the other hand, increased the PBI values to euthyroid levels although the

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the enterohepatic circulation. Both substances rapidly disappeared from the body after 15 days, 1.5 per cent of triiodothyronine and 2.5 per cent of thyroxine radioactivity remained. After injection of triiodothyronine 54.8 per cent of excreted I^{131} appeared in the urine compared with 36 per cent after injection of thyroxine. Thyroxine was selectively retained in the liver so that after 15 days more than 55 per cent of residual radioactivity was in the liver and less than 40 per cent in the carcass. Fifteen days after triiodothyronine injection virtually all radioactivity was either in the thyroid or in the carcass. This again suggests that triiodothyronine may be the active form of the hormone in the tissues.

If the circulating hormone is thyroxine or some other hydrolytic product of thyroglobulin there should exist an enzyme system in the gland itself capable of breaking down thyroglobulin by proteolysis into smaller components which can cross cell membranes. The existence of such an enzyme system has been demonstrated and its activities quantitated by DeRobertis and Nowinski [1] who measured proteolytic activity by determining the formation of tyrosine and tryptophane from the protein edestin through the action of excised human thyroid glands. They found approximately a 100 per cent increase in proteolytic activity in the thyrotoxic gland as compared with the normal and about a 25 per cent decrease in iodized thyrotoxic glands and in non toxic diffuse goiters.

Physiology

If thyroglobulin is essentially the storage form of the thyroid hormone then one would expect thyroxine to be the amino acid to which it owes all of its activity. The results of physiological assays have proved contradictory, however. While thyroxine completely relieves human myxedema it has been claimed that desiccated thyroid or thyroglobulin produces a calorigenic effect greater than can be accounted for by their thyroxine content. Thus Reid Hunt [7] showed by means of the acetonitril test that desiccated thyroid produced an effect greater than the equivalent amount of thyroxine (as iodine) in protecting mice against cyanide poisoning. This presumed superior effectiveness of thyroglobulin and desiccated thyroid cannot be due to a simple summation of the activity of diiodotyrosine and thyroxine because the former by itself has but little calorigenic effect [3, 4]. Moreover 3,5 diiodothyronine (thyroxine less two of its iodine atoms) has but 4 per cent of the activity

patients were still hypothyroid Serum cholesterol levels decreased following the administration of either compound, but the decrement bore no quantitative relationship to the degree of metabolic change Electrocardiograms reverted more rapidly to normal after triiodothyronine than after L-thyroxine therapy

The paradoxical effect of triiodothyronine on the serum protein bound iodine was also noted by Starr and Liebhold Schneck,[0g] who found that sodium levothyroxine in a dosage of 0 075 mg, orally, usually reduced radioactive iodine uptake by the thyroid of normal human subjects and that this was associated with a rise of protein bound iodine when a dosage of 0 2 mg or more was given, whereas triiodothyronine in a dosage as low as 0 008 mg orally also reduced the uptake but was associated with a decrease in serum protein bound iodine

Blackburn and his associates[70h] compared the calorigenic effects of triiodothyronine and thyroxine given intravenously to myxedematous patients The initial response to triiodothyronine appeared sooner and reached a maximum in 24 to 48 hours whereas the maximal response to thyroxine occurred in 7 to 10 days The biologic decay rate of the two substances was found to be similar and possibly identical, and therefore Blackburn and his co-workers concluded that the total calorigenic effects were substantially the same Wiswell and Asper[0i] found that triiodothyronine like thyroxine was not effective in stimulating oxygen consumption when added directly to intact tissues incubated in vitro but was more potent than thyroxine in accelerating the oxygen utilization of tissues from animals injected with these compounds and of a specific rat-heart homogenate system to which these substances have been added

Rall and his co-workers[70j] studied the metabolism of radioactive triiodothyronine L-thyroxine and D-thyroxine in subjects with and without thyroids and in one individual with a complete biliary fistula They found that the optical isomers of thyroxine were metabolized at markedly different rates although they were distributed in a similar manner in the body fluids whereas triiodothyronine was metabolized at a much faster rate than L-thyroxine and although initially it was distributed in a space similar to that of thyroxine the final value of distribution exceeded the body weight Keating and Albert[0k] compared the distribution and metabolism of radioactive triiodothyronine with that of radioactive L-thyroxine by injecting physiological doses of either compound into immature rats Both substances were distributed immediately and identically in the liver and were similarly massive in

decay to range from 0 2 to 0 4 mg of thyroxine daily indicating that the same amount would be required to maintain a normal basal metabolic rate in a patient with complete myxedema Thompson and his co-workers[8] later found that 0 3 to 0 4 mg daily of thyroxine was in fact the necessary maintenance dosage in such patients

The duration of action representing the total period of incubation activity and decay varies to some extent in accordance with the method of measurement the manner of administration and the form and amount of the hormone utilized Thus Gaddum[83] found thyroxine to be effective for 3 days when given intravenously and for 3 weeks when administered subcutaneously Salter Lerman and Means[84] found thyroxine polypeptide to be effective for 90 days whether given orally or intravenously Thompson found intravenous thyroxine active over a period of 90 days and desiccated thyroid over a period of 69 days Hughes[86] has measured the duration of action of single doses of thyroxine and desiccated thyroid in rats pre treated with thiouracil This drug prevents synthesis of thyroid hormone and results in com pensatory hyperplasia and lowered iodine content of the thyroid Administration of thyroxine or desiccated thyroid will prevent these effects and therefore the duration of their actions may be measured by ascertaining the onset of hyperplasia through the determination of increased gland weight Hughes observed much shorter duration of action even with large doses than the majority of previous investigators Small doses lasted 3 to 12 days and large doses given intra peritoneally were completely metabolized within one month Subcutaneous or intravenous injections of thyroxine were effective for as long as thyroid powder by mouth He believes this method is more accurate in measuring duration of action of thyroid hormone than the basal metabolic rate Reineke and his co workers[87] have also found this technique comparable with the standard metabolic method of performing thyroid assays or measurements of thyroid function (Figs 4 and 5)

The metabolism of thyroxine has been more carefully studied since 1944 when Joliot and his associates first described the preparation of radioactive thyroxine and its behavior in the organism[8] [8b] Albert and his co-workers[8] [8d 8] have investigated the role of the gastro intestinal tract and the liver in the metabolism of radiothyroxine by the intravenous injection of physiological doses of radioactive L thyroxine into immature male rats They observed an immediate distribution of the injected material in the blood (38 per cent of the dose) the liver (30 per cent) and the remaining tissues of the body (32 per cent) After this initial

of thyroxine The organic iodine content of the whole thyroid gland is due almost entirely to thyroxine and diiodotyrosine The calorigenic action has been claimed by Means and his associates[75, 76] to depend upon this total organic iodine rather than upon thyroxine content alone On the other hand, Palmer and Leland[77] concluded that thyroxine alone determined the calorigenic effect of thyroid, and they were able satisfactorily to explain the apparent correlation between total organic iodine of the thyroid and calorigenic activity reported by Hunt and Krogh and Lindberg[8] as due to a fortuitous parallelism between total and thyroxine iodine content Subsequently, McClendon, Foster, and Cavett,[79] after studying the calorigenic action of thyroglobulins with varying thyroxine content upon the metabolic rate of rats, concluded that the calorigenic effect of thyroglobulin depended on its thyroxine content alone Harington[60] also expresses doubt concerning the adequacy of the evidence relating the activity of the thyroid gland to its total iodine content rather than to its thyroxine iodine content

Two aspects of thyroid physiology common to all its actions are the phenomena of latency of activation and decay These manifestations are apparent either following the administration of the hormone to the thyroidless individual or following removal or atrophy of the gland When thyroxine is administered intravenously to the hypothyroid subject no discernible effect is seen until about 12 hours have elapsed[80] Following this period there develops an increased rate of metabolism which reaches a maximum on the fourth day and then gradually declines over a period of 4 to 6 weeks to the initial level The curve of activation and inactivation or decay following a given dose of thyroxine or dried thyroid gland follows a definite pattern which may be expressed mathematically with some accuracy Briefly, these curves are exponential rather than arithmetic and indicate that crystalline thyroxine must be activated before it can function The phases of activity of thyroxine in dried thyroid may therefore be divided into these three, according to Boothby (1) the period of incubation, (2) the period of increased activity, and (3) the period of decay

When the thyroid gland is removed or undergoes spontaneous atrophy, progressive inactivation or decay of the hormone takes place The same phenomena may be observed when thyroid medication is discontinued in a myxedematous patient who has received sufficient thyroid to maintain a standard metabolic rate The rate of inactivation is exponential and follows a gently sloping curve which takes 70 to 80 days for completion Plummer and Boothby[81] found the daily rate of thyroxine

decay to range from 0.2 to 0.4 mg of thyroxine daily indicating that the same amount would be required to maintain a normal basal metabolic rate in a patient with complete myxedema. Thompson and his co-workers[8] later found that 0.3 to 0.4 mg daily of thyroxine was in fact the necessary maintenance dosage in such patients.

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distribution, rapid diffusion occurred into the gastro intestinal tract, chiefly by way of bile but probably also by direct secretion At equilibrium the gastro-intestinal tract contained at any time about one half of the circulating radiothyroxine or intermediates thereof A massive recirculation of radioactivity occurred from the bowel, presumably via the portal and lymphatic drainage The rapidity of the recirculation was

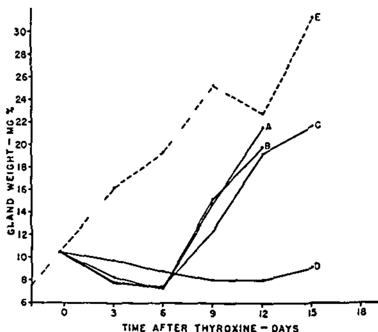


Fig 4 A comparison of the effect of single doses of thyroid hormone given by various routes to thiouracil treated rats A = 1 mg thyroxin in solution intravenously B = 500 mg desiccated thyroid by stomach tube C = 1 mg thyroxin in solution subcutaneously D = 1 mg thyroxin suspension subcutaneously E = control animals receiving thiouracil alone The initial point indicates the gland weight at the beginning of thiouracil treatment and 0 the time of thyroid hormone administration Each point represents the average of 5 or more animals From Hughs A M Endocrinology 1945 xxxvii 80 85

emphasized by the disparity between the rate at which radioactivity was secreted into the bowel, more than 100 per cent per hour, and the rate at which it left the bowel in the feces, about 3 per cent per hour Two thirds of injected radiothyroxine was ultimately excreted in feces and one third in urine Thyroxine or some derivative of it was slowly removed from blood by fixation in tissues, particularly the liver Such fixation also occurred in kidney and in other tissues at a rate of about

1 per cent per hour More than one half of the residual radioactivity was in the liver 16 days following injection

The proportion of endogenously I^{131} labeled thyroid hormone in the thyroid carcass gastro-intestinal tract and liver and the rates of movement of labeled hormone in these compartments and in the excreta

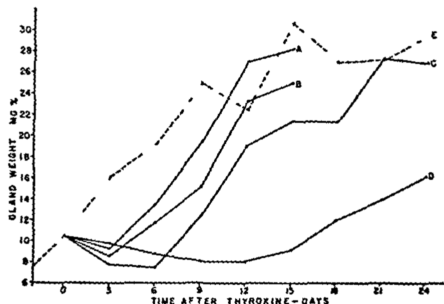


Fig 5 Effects of a single injection of thyroxin on the rate of enlargement of the thyroid glands of thiouracil treated rats A = 10 ug (solution) B = 100 ug (solution) C = 1 mg (solution) D = 1 mg (suspension) E = control animals, receiving thiouracil alone The initial point indicates the gland weight at the beginning of thiouracil administration and 0 the time when thyroxin was injected Each point represents the average of 5 or more animals From Hughs, A M Endocrinology 1945 xxxvii 280–85

were next determined under conditions of experimentally altered thyroid function in immature rats The thyroids of these rats were labeled with I^{131} and then exposed to agents or procedures that caused either liberation or retention of labeled hormone The proportions of I^{131} in *the thyroid gastro-intestinal tract and carcass were determined* Thiouracil caused an intense loss of thyroidal I^{131} and a symmetrical increase in I^{131} of the gastro intestinal tract and carcass Thyrotrophin induced similar but less intense loss of thyroidal I^{131} and a symmetrical gain in I^{131} of the carcass and gastro intestinal tract Hypophysectomy or

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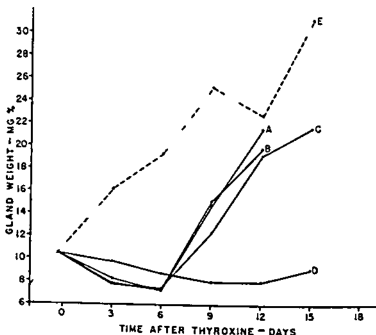


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equilibrated with serum iodide and is present as only a small percentage of the total serum iodine partly because it is disposed of rapidly and partly because its volume of distribution is comparatively large The liberated iodide present in blood is eliminated mainly in the urine Thyroid hormone is not accumulated by the thyroid and reutilized Iodide liberated in the catabolism of thyroid hormone is reaccumulated and reutilized in a normal person Approximately o per cent of the liberated iodide would be accumulated by the normal thyroid The iodide of dietary origin probably accounts for far more of the iodide utilized by the normal thyroid for synthesis of new thyroid hormone than does the small porportion of iodide liberated from the catabolism of thyroid hormone which is reaccumulated

In a later study [81] radiothyroxine was injected intravenously as a single dose in 6 patients with exophthalmic goiter The initial phase of disappearance from the blood was very rapid with a half value time of 3 hours After 1[illegible] or more hours a slow disappearance with a half value of 5 to 6 days became apparent presumably due to utilization of the thyroxine by the tissues and excretion in the urine and feces Uptake by the thyroid and excretion in the urine after administration of radio thyroxine were slower than after administration of radio-iodine and appeared to depend for the most part on the rate of release of radio iodine from radiothyroxine In these patients too the main metabolic fate of thyroxine aside from some excretion in the feces and the urine was de iodination Part of the iodide thus released was reaccumulated in the thyroid and part was excreted in the urine depending upon the ratio of the thyroidal clearance and the renal clearance About one third of the injected hormone was metabolized in 24 hours

The physiological effects of the hormone will now be considered in detail The differential analysis of its effects should not obscure the fact that in the patient the actions are multilateral and simultaneous involving many tissues and organs

Oxidative and Calorigenic Action

The first observation of the calorigenic effect of thyroid was made by Magnus Levy in 1895 when he demonstrated that thyroid deficiency was associated with a reduced metabolism and lowered oxygen consump tion [88] The fundamental oxidative processes of the body and minimal heat production are cellular phenomena which proceed independently of

treatment with thyroglobulin produced a marked increase in thyroidal I^{131} and a marked and asymmetrical decrease in the extrathyroidal I^{131}, a greater decrease occurring in the gastro intestinal tract than in the carcass Thus there exists a wide range over which the excretion of I^{131} from the body is proportional and in equilibrium with the secretion or loss of I^{131} from the thyroid When liberation of thyroidal I^{131} is inhibited by therapy with thyroglobulin, the excretion of I^{131} in feces and urine is correspondingly inhibited However, when liberation of thyroidal I^{131} is accelerated by thiouracil the fecal and urinary excretion of I^{131} is also accelerated but does not keep pace with the liberation of I^{131} from the thyroid There appears to be a ceiling beyond which the body cannot further excrete labeled thyroid hormone

Klitgaard[8f] on the other hand, in studies of the biliary and urinary excretion of radio iodine following subcutaneous injection of tracer amounts of I^{131} labeled thyroxine in normal, hypothyroid and hyperhyroid rats, found that thyroidectomized and thiouracil treated groups showed reduced biliary radio-iodine elimination, as well as diminished bile volume during the 6 hour collection period Hyperthyroid animals showed a marked increase, thiouracil treated animals a decrease in urinary excretion of radioactive iodine over a 12-hour period The radio iodine excretion in both bile and urine tended to be lower in the thiouracil treated rats than in the thyroidectomized groups

The metabolism of thyroxine has also been studied in human subjects with normal decreased and increased thyroid function[87g 87h 87i 87j] Albert and his associates[8h 87i] have studied the metabolic behavior of racemic radiothyroxine administered orally or intravenously to patients with myxedema maintained in a euthyroid state with non labeled racemic thyroxine Forty one per cent of the radioactivity was excreted in the urine and 12 per cent in the feces Eighty-five per cent of the urinary I^{131} was present as inorganic iodide and 15 per cent as organic I^{131}, consisting of both thyroxine and diiodotyrosine The bulk of thyroid hormone is therefore de iodinated and excreted in the urine as iodide On the basis of these studies Albert and his co workers formulated the following highly tentative picture' of the metabolism of thyroxine under normal conditions On entry into the circulation thyroxine is confined at first to the plasma from which it is transferred to the tissues of the body, including especially such organs as the liver, and becomes equilibrated with the thyroid hormone already present in tissue In the tissues thyroid hormone is catabolized mainly to iodide and to a minor extent is split apparently at its ether linkage The iodide liberated becomes

The calorigenic action of the thyroid hormone has been clearly traced to the tissues but the exact mechanism by which it alters metabolic processes is unknown It is probably not a true catalyst because it lacks uniformity of effect among various tissues and because its effect is delayed in appearance Both Gordon and Heming and earlier Dye[93] suggested that it works by increasing the effectiveness of or by stimulating the synthesis of various respiratory enzymes

Thyroid in Thermoregulation

In its oxidative function the thyroid contributes significantly to total heat production In addition the gland has a definite relation to the actual regulation of the body temperature Prolonged exposure to cold results in increased thyroid activity[94] This has been most satisfactorily demonstrated by measuring the fixation of radio iodine in the rat s thyroid following exposure to varying temperatures[95] Exposure to freezing temperatures (0 to 2) produced thyroid stimulation after 7 days which reached a maximum after 26 days and was absent after 40 days There was a nearly threefold increase in the uptake of radio-iodine for thyroxine synthesis at the time of maximal stimulation by the cold Heat lessened thyroid activity but the effect of heat was far less prominent than that of cold

The thermoregulatory function of the thyroid is dependent upon both the hypophysis and the adrenals According to Uotila[96] hypophysectomy abolishes the response of the thyroid to cold Epinephrin has a calorigenic effect which is greatly increased by the thyroid hormone[94] Dinitrophenol in amounts calorigenically equal to thyroxine increased the hypothermia of mice subjected for 1 hour to an environmental temperature of 5 C whereas thyroxine decreased such hypothermia[97]

The role of the thyroid in thermoregulation is also reflected in changes in the gland occurring seasonally Riddle[98] found the thyroid of pigeons to be larger in winter and smaller in summer Earlier Seidell and Fenger[99] demonstrated a threefold increase in iodine content of the thyroid gland of various animals during the summer months thus indicating reduced physiological activity Kendall and Simonsen[100] similarly found increased iodine and thyroxine content of the gland during the summer and a decrease during the winter Dempsey and Astwood[101] have determined the rate of hormone secretion at various environmental temperatures by measuring the amount of thyroxine

thyroid activity, but the thyroid, in the words of Marine, provides the means through its iodine-containing hormone, of maintaining a higher level of metabolism than would otherwise obtain'[89] In other words, the thyroid forces an increased rate of oxidation within the cell There is production of heat with oxidation, and thus the oxidative effect of thyroid is known as its calorigenic action

The calorigenic action of thyroid may be readily measured in the organism by the determination of oxygen consumption or carbon dioxide production This is the method of indirect calorimetry and is the basis of clinical metabolism testing wherein the oxygen consumption is measured for an exact unit of time and compared with standard values for normal individuals One may however, with a calorimeter measure the heat production of the organism by utilizing the method of direct calorimetry, this is too cumbersome for clinical purposes but has been of fundamental importance in research on energy metabolism

In the resting fasting state the thyroid accounts for slightly less than half of the total heat output or oxygen consumption, since total thyroidectomy or myxedema decreases the basal metabolic rate by about 40 per cent The organism lives and respires but the oxidative fires burn low

That the thyroid hormone produces its calorigenic effect by direct action on the tissues or the tissue cells has been established in many ways Aub and his associates[90] showed that the hypermetabolism induced by thyroxine could not be explained by muscular activity or tonus and was unaffected by adrenalectomy Studies on the whole animal because they are complicated by nervous and interhormonal relationships have to some extent been supplanted by observations on excised organs or tissues in further efforts to understand the exact way in which the thyroid exerts its oxidative effect

Myer McTiernan and Aub[91] showed that liver slices from thyroxinized mice had an increase in oxygen consumption and in anerobic glycolysis They also demonstrated that the oxygen consumption of denervated and normal kidneys is similar in thyroxinized dogs The nervous system is thus not essential for the effect of thyroxine on tissue metabolism The direct effect of thyroxine upon tissues is not universal since these same workers found no effect or a depressing effect on the oxygen consumption of malignant tissues excised from thyroxinized mice In similar fashion Gordon and Heming[92] found that administration of thyroid and thyroxine caused significant increases in the oxygen consumption of liver kidney diaphragm and heart of the rat but they observed no effect on spleen, brain or testis

The calorigenic action of the thyroid hormone has been clearly traced to the tissues but the exact mechanism by which it alters metabolic processes is unknown. It is probably not a true catalyst because it lacks uniformity of effect among various tissues and because its effect is delayed in appearance. Both Gordon and Heming and, earlier, Dye[93] suggested that it works by increasing the effectiveness of or by stimulating the synthesis of various respiratory enzymes.

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necessary to maintain normal thyroid weight in thiouracil treated rats With this method there was further confirmation of the view that cold increases thyroid activity and hormonal synthesis while heat does the reverse Similarly Turner and Turner,[10] utilizing the Warburg technique showed that the same was true when the thyroid tissue of guinea pigs was studied in vitro Mansfeld [103] has recently summarized studies which, if confirmed, would establish the thyroid gland as of ascendent importance in thermoregulation By serum transfer experiments he showed that temperature regulation against heat and cold was associated with the secretion of substances which depressed oxidation in normal animals and was dependent on an intact thyroid gland He found the thyroxine sensitivity of the organism greatly decreased during the spring and summer thyroidectomy abolished this sensitivity Two crystalline substances, thermothyrin A and B, were isolated from the gland Thermothyrin A was produced throughout the whole year if the organism was exposed to high temperatures, whereas thermothyrin B was produced during the summer months regardless of external temperature Both of these substances were antithyroidal in their action

Effect on Growth and Metamorphosis

The precise role of the thyroid in growth is not entirely clear because of its interrelation in this function with the anterior pituitary In human and animal cretinism stunting of growth regularly occurs yet there is much evidence that the thyroid hormone serves an auxiliary rather than a primary function in growth Rats and goats thyroidectomized in the first week of life quickly become static in weight and anatomical differentiation and present the usual features of cretinism [104, 10, 106] The effects of thyroidectomy appear earlier and are more pronounced in accordance with the age and weight of the animal Rats thyroidectomized at birth showed marked retardation of growth and maturation but according to Scow and Simpson [107] did not develop the growth stasis reported by Salmon [104, 10] Instead they showed a very slow but continuous increase in weight and skeletal size In addition these workers noted delayed appearance of secondary ossification centers, low oxygen consumption, retarded change from infant to adult type of hair delayed opening of the eyes and delayed eruption of the teeth (Figs 6 and 7)

Growth in the thyroidectomized animal can be maintained or restored

to normal by the administration of thyroid gland substance [108] thyroxine [109] or artificial thyroprotein [106]

The administration of anterior pituitary extract to rats thyroidectom-



Fig 6 Triplet kids Center animal normal right and left hand animals thyroidectomized at [illegible]0 days old Photograph taken 13 weeks after operation (Sutherland Simpson) From Harington C R The thyroid gland its chemistry and physiology Oxford University Press, London 1933

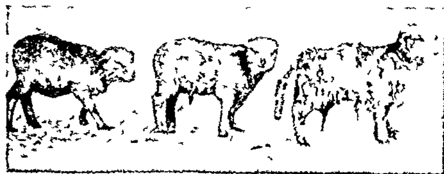


Fig 7 Three lambs thyroidectomized at the age of 3-4 weeks Note pot belly of left hand animal and poor condition of fleece in all Photograph taken 8 weeks after operation (Sutherland Simpson) From Harington C R The thyroid gland its chemistry and physiology Oxford University Press London 1933

ized at birth will not induce gain in weight skeletal growth, or gonadal development, according to Salmon[110] Her view is that the thyroid is necessary in the early postnatal period for the development of the capacity of the organism to respond to other hormones that influence growth The age of the animal at the time of thyroidectomy is therefore a critical factor, since it is established that anterior pituitary extract is effective in promoting the growth of animals thyroidectomized in the later postnatal period[111] Rowlands[109] has also noted the failure of pituitary injection to overcome growth retardation in the very young thyroidectomized animal Scow and Simpson,[11] utilizing thyroidectomized newborn rats, found that the response to hypophyseal extracts did not depend upon the age of the animal and that the capacity to grow with pituitary stimulation alone was present at birth

The role of the thyroid in growth is apparently that of a synergism to the more important stimulation provided by the growth component of the anterior pituitary This synergism was first observed by Smith[113] who noted greater growth with pituitary and thyroid extracts than with the former alone in hypophysectomized and thyroidectomized rats The synergistic action of thyroid on growth has been confirmed by Evans and his co-workers[11, 114] who observed abnormally large growth increments when thyroxine was administered with anterior pituitary extract to thyroidectomized animals They also found that thyroid did not stimulate growth in animals deprived of both hypophysis and thyroid gland thus again indicating the primacy of the anterior pituitary in growth Additional proof of the synergy between thyroid and hypophysis in the growth process is evidenced in the increased growth rate of normal young mice given thyroxine[11] or thyro active iodo casein[116] and in the increased speed of growth in juvenile thyrotoxicosis[117]

Growth involves either increase in cell size or cell number or both The end result of growth will therefore be a larger or a more differentiated organism The thyroid plays a significant role in these processes, but more so in differentiation than in growth Gudernatsch,[118] while studying metamorphosis in tadpoles observed that thyroid accelerated this process in a remarkable fashion This observation was confirmed by Uhlenhuth[119] who found that small quantities of thyroglobulin led rapidly to precocious metamorphisis of tadpole larvae Later Allen[1 0 1 1] demonstrated that thyroidectomized tadpoles will not metamorphose Finally thyroid was found to induce the metamorphosis of axolotls, which usually remain in the larval condition without further matura

tion[1] These striking effects of thyroid upon differentiation result essentially in the induction of precocious growth

The influence of thyroid upon differentiation is both so specific and so sensitive that it may be used for detecting thyroidal activity in biological materials through measuring metamorphosis of either tadpoles or axolotls[1-3]

Thyroid and Water Exchange

Knowledge of the relation of the thyroid to water exchange has been accumulated chiefly through studies on myxedematous patients and thyroidectomized animals because the effect of the thyroid hormone on water metabolism is so clearly seen during the initial phase of its administration to the hypothyroid subject

In myxedema there occurs a low plasma volume[1.4, 1.5] and an increased plasma protein associated with an increase in extracellular fluid in the tissues generally whereas in thyrotoxicosis the blood volume is increased[1.6] The increased tissue fluid that characterizes myxedema differs from all other types of edema fluid in that it has a high content of a mucinous protein Boothby and his co workers[1.7] after studying the effects of thyroxine administration upon the nitrogen metabolism of normal and myxedematous subjects concluded that the edema fluid in myxedema had twice the protein content of serum This extra protein they regarded as reserve or deposit protein and found it to be eliminated or oxidized when thyroid was administered Along with this protein diuresis following thyroid administration there occurs a diuresis of water of considerable magnitude The fluid so diuresed contains a large excess of sodium over potassium and Byrom[1.8] has therefore concluded that the fluid is contributed mainly by the extracellular compartments of the body In the normal subject thyroxine causes loss of body protein associated with loss of water containing more potassium than sodium and so presumably derived from the intracellular water stores This simple view of the relative roles of potassium and sodium in intracellular and extracellular water exchange has however been criticized in a general way by Darrow[1.9] who notes that these ions are also in a dynamic state in which no part of the body is inaccessible to them The least we can do is to cease speaking of the distribution of various ions as if they were always excluded from certain phases of body water

Another factor contributing to the increased tissue fluid and decreased plasma volume of myxedema is the great increase in capillary perme-

ized at birth will not induce gain in weight, skeletal growth, or gonadal development, according to Salmon.[110] Her view is that the thyroid is necessary in the early postnatal period for the development of the capacity of the organism to respond to other hormones that influence growth. *The age of the animal at the time of thyroidectomy is therefore* a critical factor, since it is established that anterior pituitary extract is effective in promoting the growth of animals thyroidectomized in the later postnatal period.[111] Rowlands[103] has also noted the failure of pituitary injection to overcome growth retardation in the very young thyroidectomized animal. Scow and Simpson,[11] utilizing thyroidectomized newborn rats, found that the response to hypophyseal extracts did not depend upon the age of the animal and that the capacity to grow with pituitary stimulation alone was present at birth.

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depletion The important factors for consideration are three acidosis and negative nitrogen balance a catabolic effect of thyroid hormone on bone, and the possibility of an associated hyperparathyroidism

A negative nitrogen balance and tissue acidosis may cause hyper calcinuria Many thyrotoxic patients have a negative nitrogen balance and this fact must be contributory in some instances With a negative nitrogen balance there is increased phosphate and sulphate excretion as the patient is burning body protein and thus has the equivalent of an acid forming diet [13, 136] which in itself increases calcium excretion The negative nitrogen balance produced by fasting causes urinary calcium excretion comparable to that of hyperthyroidism

A secondary cause of calcium depletion in thyrotoxicosis is the possible catabolic effect of thyroid hormone on bone It is true that the calcium loss is far greater proportionally than the rise in metabolic rate and that there is no calcium loss in non thyrogenous hypermetabolism These facts do not exclude a direct effect of the hormone on calcium deposits in the bone and in truth one is still left with this mechanism as the best explanation of the disturbed calcium metabolism [13]

Finally to be considered is the hypothesis of an associated hyperpara thyroidism in all cases of thyrotoxicosis Clinically this association rarely occurs [137] Hansman and his associates [138, 139] have argued that the increased calcium and phosphorus excretion in thyrotoxicosis is due to concomitant hyperparathyroidism for these reasons (1) there is com plete lack of parallelism between the basal metabolic rate and calcium phosphorus exchange (2) roentgen ray therapy to the hyperplastic thyroid alters the calcium phosphorus balance favorably while leaving the metabolic rate unaffected, because of the greater sensitivity of the parathyroids to irradiation This is an argument of indirection which may be valid and yet if true is contrary to the usual finding of hyper calcemia in proved hyperparathyroidism In a study of parathyroid function in hyperthyroidism utilizing the rise in serum calcium of the rabbit as the method of assay, Gilligan Volk and Gargill [140] found evidence of parathyroid hyperfunction in less than half the cases studied Cope and Donaldson [141] were able to demonstrate a marked increase in calcium and phosphorus excretion in a patient with coexistent hypo parathyroidism and thyrotoxicosis If parathyroid activity is increased in hyperthyroidism its physiological pattern of activity is probably some-what different from that seen in hyperparathyroidism alone The different pattern of response to thyroid and parathyroid hormone has again been emphasized by Logan Christensen, and Kirklin [14] who found that in

ability demonstrated by Langer [130] in this disease This altered permeability is returned to normal by thyroid administration, indicating that the hormone helps maintain normal capillary permeability

Thyroid Hormone and Mineral Metabolism

The effect of the thyroid hormone on calcium and phosphorus metabolism has been extensively studied Many early investigations suggested an excessive calcium and phosphorus loss but were inconclusive because of failure to control the intake In 1910 Towles [131] clearly demonstrated that thyrotoxic patients with a negative nitrogen balance also had a loss of calcium Aub and his co-workers,[13, 133] however, in more comprehensive studies of this subject, conclusively established the marked increases in both calcium and phosphorus excretion in toxic goiter The percentile increased loss was far greater than the increased basal metabolic rate, and elevated metabolic rates from other than thyroid disease were not associated with increased calcium and phosphorus excretion The ratio of excretion of calcium to phosphorus strongly suggested that the extra loss came from calcium phosphate in the bones This was further corroborated by roentgenological evidence of bone demineralization In myxedema, on the other hand, there was marked decrease in calcium excretion These profound changes in calcium and phosphorus exchange in thyrotoxicosis did not alter the blood levels of these minerals

The increased calcium and phosphorus excretion in thyrotoxicosis occurs both through the kidneys and through the intestines and is reflected in elevated urine and fecal values This contrasts strikingly with the mineral exchange in hyperparathyroidism, where the increased excretion is entirely through the kidneys A satisfactory explanation of the large fecal calcium in thyrotoxicosis has been offered by Althausen and his co workers [134] who studied calcium exchange in the rat s intestines They concluded that in experimental hyperthyroidism there was interference with normal reabsorption of intestinally excreted calcium This was ascribed to two factors (1) the increased food ingestion usually occurring in thyrotoxicosis interferes with normal reabsorption, and (2) increased intestinal peristalsis accelerates the passage of feces to such an extent that there is further interference with reabsorption

As the heightened excretion of calcium and phosphorus occurs in the urine as well as in the feces other mechanisms must exist that cause this

magnesium was low or absent This change in magnesium partition was not associated with changes in the total serum magnesium

These findings were confirmed and extended by Dine and Lavietes[152] who felt that the serum level of the bound magnesium might be a useful index of thyroid function They suggested further that the magnesium might be attached to the thyroid hormone or be part of an associated enzyme system This interesting development has failed of confirmation by Cope and Wolff[153] and Bissell[154] who found no important deviation from normal in the magnesium partition of hyperthyroid subjects

The studies on magnesium partition in thyroid disease have suggested that bound magnesium unlike bound calcium is physiologically active but this knowledge has as yet no practical applications

Thyroid and Protein Metabolism

The role of the thyroid hormone in protein metabolism in normal persons has not been determined Chief attention has been given to the nitrogen balance in myxedema and thyrotoxicosis and to the alterations in creatine and creatinine metabolism occurring in these conditions If adequate calories from carbohydrate and fat sources are available thyrotoxic patients may be maintained on low protein diets with the minimal nitrogen excretion characteristic of normal persons[155]

In thyrotoxicosis urinary nitrogen is increased[156] whereas it is decreased in myxedema[157] Important changes also occur in creatine and creatinine metabolism Creatine is normally low or absent in the urine of adults on creatine free diets but in hyperthyroidism it is excreted in abnormal amounts Shaffer[158] who first noted this alteration also found decreased creatinine excretion in the same group of patients Both of these changes have been confirmed by many later investigators[159, 160] The creatinuria disappears with control of the hyperthyroidism by iodine[161] although the altered creatine metabolism may persist for many weeks following thyroidectomy[162] In myxedema as in normal persons there is no creatinuria but evidence of abnormalities of the creatine metabolism is adduced by the fact that the spontaneous creatinuria of normal children is reduced or absent in cretinism and juvenile myxedema[163, 164, 165]

Richardson and Shorr[166] and later Thorn[167] found a decreased tolerance to ingested creatine in thyrotoxicosis and an increased tolerance in myxedema suggesting a fundamental alteration by thyroid activity in

hyperthyroid dogs there was a marked increase in renal calcium excretion with normal serum calcium levels and an inconsistent effect on phosphorus metabolism The parathyroid hormone, on the contrary, caused an immediate rise in urinary phosphorus with a drop in serum phosphorus and a slow rise in serum calcium and calcium excretion

Robertson [143] rejects the hypothesis of coexisting hyperparathyroidism, first on the ground that in his observations serum calcium tends to be low rather than high in thyrotoxicosis, and secondly because of the normalizing effect of iodine and thyroidectomy upon calcium excretion He advances the theory that thyroid hormone typically lowers the renal threshold for calcium by direct action on the kidney The lowering of the threshold results in a fall in serum calcium concentration, which causes an increased mobilization of calcium from the bones in the blood stream In hypothyroidism, conversely the renal threshold is raised and there is a subnormal excretion of calcium This is an attractive theory based upon rather small differences in serum calcium levels between normal subjects and thyrotoxic patients

Regardless of the mechanism there is no question of the fact of calcium and phosphorus loss in thyrotoxicosis This is further evidenced in skeletal demineralization which can be demonstrated by roentgen ray examination of the bones [144] Osteoporosis is not an invariable accompaniment of the thyrotoxic state except in long standing cases [14] In addition the age of the patient [146] and the opportunity of achieving calcium and phosphorus balance by adequate mineral and vitamin D intake are factors of importance [147] Osteoporosis may be severe enough to result in spontaneous fractures [14, 148] or so slight that it can be detected only by simultaneous radiograms of the normal and the thyrotoxic patient on the same x ray film [13] In most patients it cannot be demonstrated [147]

The large excretion of calcium and phosphorus in toxic goiter led Tibbetts and Aub [149] to investigate magnesium metabolism in that disease Magnesium like calcium is present in small amounts in the blood and is also a constituent of bone These authors found no increased magnesium excretion in two patients with thyrotoxicosis but they did not study the concentration of magnesium in the serum Subsequently Soffer and his associates [1 0, 151] investigated the magnesium content of the blood in hyperthyroidism with special reference to the ratio between diffusible and bound or non diffusible fractions They found a definite increase in the bound magnesium in 35 out of 50 cases of Graves disease Treatment with iodine or thyroidectomy caused marked lowering of the bound magnesium and in myxedema, clinical or experimental the bound

tion of thyroid for a short period led to temporary diabetes or to permanent diabetes if the administration was long continued In the latter instance irreversible changes in the beta cells of the islets of Langerhans were demonstrable Houssay also found that islets previously damaged by antero hypophyseal injections were more sensitive to thyroid treatment However the diabetogenic action of thyroid was not as great as that of alloxan or anterior pituitary extracts since it did not take effect until there had been diminution in the pancreatic mass or actual damage to the islets This diabetogenic action continued after removal of the gonads thyroid and adrenal medulla In animals already diabetic as in human beings thyroid ingestion always increased the severity of the disease and shortened survival by increasing glycosuria ketonuria and insulin need

Thyroid feeding in rats can sensitize the islets to the diabetogenic action of alloxan according to Martinez[1] whose figures are of interest there was an average lethal dose of [illegible]5 mg of alloxan for the hyperthyroid rats of 54 mg for the controls and of 74 mg for the thyroidectomized animals showing the increased resistance to the drug in hypothyroidism

This problem has been approached by Soskin[173] in a different fashion Through the use of hypophysectomized dogs he was able to avoid the difficulties of attempting total thyroidectomy in dogs who often have aberrant thyroid tissue Secondary atrophy of the thyroid resulted from hypophysectomy and with it was a marked hypoglycemia in the fasting state Administration of thyroxine restored and maintained normal blood sugar values thus proving that this secondary atrophy plays a significant role in the carbohydrate disturbance following hypophysectomy Herring and his co-workers[174] however found no such effect of thyroxine on the blood sugar and glycogen stores of fasted hypophysectomized rats and Lukens and Dohan[175] using partly pancreatectomized cats found no great effect of thyroxine or thyrotropic hormone on carbohydrate metabolism and no modification of diabetes by thyroidectomy There are apparently great species differences with regard to the effect of the thyroid on carbohydrate metabolism

The second effect of the thyroid in relation to carbohydrate metabolism is found in its specific action in altering the absorption of sugars from the intestinal tract Thyroid ingestion in normal rats causes greatly increased absorption of glucose while thyroidectomy causes a reduced rate of absorption[1 6] This increase is probably due to a direct action on the mucosa of the digestive tract with stimulation of phosphorylation This is the important intermediary step in the conversion of starch or glycogen

the capacity of the organism to metabolize creatine Tierney and Peters[166] however, could detect no important change in creatine metabolism, though agreeing that hyperthyroidism induces or increases creatinuria They found that creatine, unlike creatinine had a definite renal threshold above which excretion into the urine occurred In thyroxinized rats Bodansky[167] and Sure[168] have demonstrated marked reduction in muscle and heart creatine content, and more recently Wang[169] observed in rabbits that thyroxine treatment reduced muscle creatine and phosphocreatine content and that thyroidectomy produced opposite effects Wang also found that thyrotoxicosis induces excess creatinuria but that this was transitory and soon decreased and approached normal levels At the same time creatinine elimination in the urine was very much reduced probably owing to a creatine-sparing process He points out that these relations of urinary creatine and creatinine are important in explaining the lack of correlation between the level of the basal metabolic rate and creatinuria and they eliminate the possibility of utilizing creatinuria as a measure of the thyrotoxicosis

Wilkins and Fleischman[170] on the basis of careful human experiments, concluded that the essential action of thyroid is creatinolytic, it facilitates loss of creatine from the muscles and liberates it in excess, thereby diminishing the stores of creatine and phosphocreatine Thus metabolic conversion in thyrotoxicosis proceeds through normal channels but at an accelerated rate In myxedema there is storage of creatine and phosphocreatine in the muscles

Thyroid and Carbohydrate Metabolism

The occurrence of glycosuria and hyperglycemia in thyrotoxicosis as well as the aggravation of diabetes by thyroid overactivity and its amelioration by thyroidectomy, have led to many studies on the relation of the thyroid hormone to the metabolism of carbohydrates This relation is manifold and occurs primarily through (1) direct and specific action on the pancreas (2) alteration of intestinal absorption (3) changes in the body glycogen stores and (4) increased carbohydrate utilization by the tissues

The action of the thyroid on the pancreas has been most informatively studied by Houssay[171] in dogs An extreme degree of thyroid feeding to these animals did not produce diabetes when there was an intact pancreas Following subtotal pancreatectomy, however, similar administra

just as it plays a role in protein and carbohydrate metabolism Epstein and Lande[185] observed an increase of the blood cholesterol in myxedema and a decrease in hyperthyroidism Hurxthal and his associates[186 187 188 189] confirmed and extended these observations firmly establishing the important effect of thyroid hormone upon cholesterol levels in the blood The cholesterol concentration was found to be an especially sensitive indicator of hypothyroidism whereas the deviations produced by hyperthyroidism were less constant Following total thyroidectomy for *chronic heart disease*[190] *appreciable rises in the blood cholesterol occurred* within 1 week increasing steadily to maximum values at the end of 4 weeks In this group of patients the cholesterol was at times a more accurate measure of myxedema than the basal metabolic rate This has also been our experience in spontaneous myxedema In the evaluation of juvenile hypothyroidism the determination of blood cholesterol has been of value[191] especially in view of the difficulties encountered in determining the basal metabolic rate in children

Alterations in the concentration of blood cholesterol reflect parallel changes in all the lipids of the blood cholesterol determination serving as a convenient measure of these changes because it is readily estimated in the laboratory The total lipids of the blood include neutral fat fatty acids free cholesterol cholesterol esters and phospholipids Bing and Hechscher[19] found an increase in the total lipids in myxedema and a decrease in hyperthyroidism Boyd and Connell[193 194] studied the effect *of hyperthyroidism in fat metabolism by careful fractionation of the* blood lipids and found significant decrease in all of the lipids except neutral fact which remained unchanged The lipid values returned to normal with control of the thyrotoxic state In a study of the serum lipoids particularly cholesterol phosphatides and fatty acids in hypothyroidism Gildea Man and Peters[195] found these fatty constituents of the blood readily affected by changes in the amount of thyroid hormone Myxedema was associated with high values which reverted to normal following thyroid administration These workers concluded that normal cholesterol values in the blood excluded the diagnosis of hypothyroidism

While the estimation of the cholesterol level of the blood has established itself as a valuable laboratory aid in the diagnosis of myxedema this procedure has been found less dependable in the diagnosis of thyrotoxicosis This is due to the considerable range of values found in normal persons a range so great that no significance can be attached to a single observation unless it is extremely abnormal However, the variability

to glucose, or the reverse in which phosphate is bonded to glucose The accelerated absorption of sugar readily explains the hyperglycemia the high glucose tolerance curves and the postprandial glycosuria found in thyrotoxicosis In myxedema on the other hand the slow intestinal absorption of sugar leads to low sugar tolerance curves Thyroxine also acts to augment maximally the rate of glucose absorption by the renal tubules[177] where again it is believed to exert its effects by activation of the enzyme systems involved in the transfer of phosphate energy

The effect of thyroid on liver glycogen varies in accordance with the amount of food ingested and the store of glycogen present in the liver If thyroxinized animals eat adequately to maintain weight they will form and store glycogen[178] This may be dependent upon the intake of B vitamins since it has been demonstrated[179] that hyperthyroid animals receiving subminimal amounts of B vitamins will lower their glycogen reserves while maintaining normal glycogen storage on full intake of B vitamins The idea that thyroid makes liver glycogen labile depends for its proof upon the effect of epinephrin on liver glycogen since this hormone produces glycogenolysis more readily in hyperthyroid than in normal animals This is true but depends further on the liver glycogen stores[180] Epinephrin hyperglycemia in thyroxinized animals is exaggerated so long as glycogen is present in the liver but disappears with depletion of the glycogen stores it may even lead to hypoglycemia[181] Furthermore in like manner Long[160] has pointed out that the supposed antagonism of the thyroid hormone and insulin is dependent upon liver glycogen stores since thyroid extract decreases insulin hypoglycemia while liver glycogen is present but eventually leads to glycogen depletion and fatal hypoglycemia from minimal amounts of insulin The glycogen content of skeletal and cardiac muscle has also been shown to respond to the thyroid hormone in much the same way as does liver glycogen[18, 183] decreasing in amount with hyperthyroidism

Finally to be considered is the action of the thyroid in increasing the utilization of carbohydrate by the tissues Mirsky and Broh Kahn[184] using eviscerated animals showed that the extrahepatic tissues utilize more carbohydrate when thyroid is fed Thus in hyperthyroidism one may properly postulate an increased removal of glucose from the blood because of increased carbohydrate oxidation in the tissues

Thyroid and Fat Metabolism

The thyroid hormone influences the intermediary metabolism of fats

produces no changes in blood cholesterol[199] Similarly depression of the basal metabolic rate by non thyrogenous conditions is not accompanied by alterations in blood cholesterol levels[90] (Fig 8)

Animal experiments have not provided illuminating answers with respect to the mechanism by which blood fat levels are changed in thyroid disease In the dog thyroidectomy elevates the blood lipids[91] provided the nutrition of the animal is adequate[5] Hypophysectomy by itself has little effect but produces a high concentration of blood lipids when followed by thyroidectomy[13] In the monkey thyroidectomy has no measurable effect on cholesterol levels[94, 90, 96] The hypothyroid rat according to Handler[97] has a marked increase in liver cholesterol and a slight increase in neutral fat whether on a normal or a choline deficient diet Thyroid feeding reverses this process The effect of thyroid is most marked on the liver cholesterol fraction Handler believes that the thyroid may specifically control cholesterol metabolism through regulation either of its synthesis and utilization or of transport and distribution

Thannhauser and Schmidt[8] in a recent review of fat metabolism conclude that the reason for the increase of serum cholesterol in hypothyroidism is not known

Thyroid Function and Vitamin Metabolism

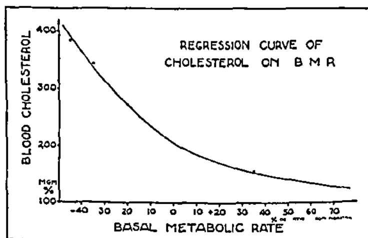
Just as the thyroid hormone plays an important role in the intermediary metabolism of proteins carbohydrates and fats so too has it significant interrelations with vitamin metabolism The large increase or decrease in energy metabolism occasioned by elevation or depression of the thyroid function in itself is contributory to this interplay because vitamin need in many instances runs parallel with energy metabolism Clinically the two outstanding examples of the effect of the thyroid on vitamin metabolism are seen in the striking deficiencies of vitamin B complex induced by thyrotoxicosis and in the disorder of vitamin A metabolism evidenced by the carotenemia of myxedema

Drill[98] has considered in great detail the relations between each vitamin and the thyroid gland Vitamin A and several components of the B complex have been most clearly related to changes in thyroid function Experimentally an antagonism between thyroxine and vitamin A has been demonstrated in amphibia Vitamin A retards the usual acceleration of metamorphosis in tadpoles and in salamander larvae produced by thyroxine[10, 11, 1] In hyperthyroid rats there is increased utilization of

in a normal person over months or years is far less than that of a group and in fact is relatively characteristic for the individual[196] In thyrotoxicosis the cholesterol level is usually depressed, but this decrease, unless marked, may not become apparent until control of the thyrotoxicosis has returned the cholesterol and lipid level to the individual's normal values For the same reason concentrations within the normal range may occasionally be found in myxedema with eventual depression to the individual s normal as thyroid administration relieves the hypothyroid state[197]

Foldes and Murphy[198] have studied the distribution of cholesterol, cholesterol esters and phospholipid phosphorus in the blood in thyroid disease confirming the earlier work of Boyd and Connell, proving that the alterations occurred primarily in the plasma, with relatively little change in the cell lipid values They noted a constant decrease in the plasma phospholipid phosphorus in hyperthyroidism

In man the role of the thyroid hormone in lipid metabolism appears to be specific since elevation of the basal metabolic rate by dinitrophenol



The Relationship between Blood Cholesterol and Basal Metabolic Rate as Reported in the Literature

The number of observations represented by each point in the figure are

Basal metabolic rat	−40	−30	−20	−10	0	+10	+20	+30	+40	+50	+60	+70	+80
N mbe f b si	4	6	15	13	20	14	21	20	21	16	16	17	12

Fig 8 From Cutting W C Rytand D A and Tainter M L Jour Clin Invest 1934 xiii 547 52

Vitamin C needs are apparently increased by thyroid feeding, and the tissues are depleted of their vitamin C content[illegible] In thyrotoxic patients vitamin C excretion has been found decreased even with a high intake of ascorbic acid thyroidectomy alone serving to cause normal excretory values[illegible]

The relation of thyroid fuction to the metabolism of other vitamins has been studied less extensively As yet these studies have not yielded important physiological or clinical applications[illegible]

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vitamin A[13] as well as increased requirements for vitamin A.[14] This has been demonstrated by the production of xerophthalmia in thyroxinized rats on a normal intake of vitamin A. There is considerable animal research tending to show that antecedent use of vitamin A will partly antagonize the calorigenic action of thyroid or thyroxine. On the other hand, once hypermetabolism has been produced by either thyroid or thyroxine, vitamin A has no antithyroidal effect either in animals[15, 16, 17] or in patients with hyperthyroidism.[18]

The development of xerophthalmia in thyroidectomized rabbits ingesting a normal diet[19] ultimately led to the finding that the thyroid hormone is necessary for the conversion of one molecule of carotene into two molecules of vitamin A and for the hepatic storage of vitamin A.[20] Thus in cretinism low blood values of vitamin A were unchanged by the administration of carotene.[21] Carotenemia is a usual concomitant of human myxedema[22, 23, 24] and is corrected by the administration of thyroid. The disturbed metabolism of vitamin A is also reflected in the impaired dark adaptation of hypothyroid patients, as vitamin A is essential in the regenerating of the visual purple.[25]

The relation of the B vitamins to thyroid function is perhaps simpler than that of vitamin A. With hypermetabolism there is an increased need for certain of the B vitamins, particularly thiamine, pyridoxine, pantothenic acid and probably riboflavin. Hyperthyroid dogs on a yeast-free diet developed anorexia twice as fast as normal dogs on the same diet. The administration of vitamin B concentrate stopped the weight loss and induced weight gain.[26] It was also found that the feeding of thyroid substance to pigeons increased their vitamin B requirements.[27] Potent vitamin B concentrate served to prevent weight loss in thyroxinized rats.[28]

Further studies of the B complex have indicated the components that are important in relation to thyroid function. Drill and Sherwood[29] observed that thiamin stopped weight loss in thyroxinized rats by increasing caloric intake but was ineffective in causing weight gain. When, however, calcium pantothenate and pyridoxine were added to the thiamin, there ensued gain in weight.[30] Therefore it may be concluded that thiamin, pyridoxine and pantothenic acid are required in increased amounts in experimental thyrotoxicosis. The experimental evidence for increased need of riboflavin in hyperthyroidism is not so definitely established. In thyroxinized rats there is excessive excretion of riboflavin in the urine[31] and this is associated with decreased tissue content of riboflavin and large losses of body weight.

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PART II

THE INTERRELATIONS OF THE THYROID WITH THE OTHER ENDOCRINE GLANDS

The reciprocal relations of the thyroid with other endocrine glands are just as important as its own chemistry and physiology. There can be no adequate understanding of clinical disturbances of thyroid function without knowledge of the factors that control this endocrine equilibrium. The relation with other glands is most importantly manifested in what Salter[1] has termed the pituitary thyroid axis for the pituitary gland plays a dominant part in the control of thyroid development and function.

THE INTERRELATION OF THE THYROID AND THE ANTERIOR PITUITARY

The earliest observations on the relation between the pituitary and the thyroid indicated that the integrity of the thyroid affected pituitary function many years elapsed before it became plain that there was a significant reciprocal interaction between the two glands. Niepce in 1851 in the course of observations on goiter and cretinism found striking enlargement of the pituitary gland in goitrous cretins. In 1889 Rogowitsch[3] observed great enlargement of the anterior pituitary following total removal of the thyroid in rabbits and dogs. Schonemann[4] confirmed both these observations when he found that patients or animals with large non functioning goiters had hypertrophied anterior pituitary glands. Subsequent observations have shown that myxedema and cretinism are regularly associated with significant pituitary enlargement[5, 6].

The effect of hypophysectomy in producing atrophy and hypofunction of the thyroid was first demonstrated by Ascoli and Legnani[7] in 1911 and confirmed in the following year by Aschner. The acceleration of tadpole metamorphosis by thyroid gland administration first observed by Gudernatsch[9] afforded a new method for studying thyroid function. Hypophysectomy in tadpoles was shown by Adler[10] in 1914

to prevent normal metamorphosis by causing thyroid atrophy Subsequently Smith[11] and, independently, Allen[12] found that extirpation of the pituitary anlage in tadpoles caused failure of the thyroid to develop normally, with secondary arrest of maturation unless thyroid was administered By transplantation experiments with adult pituitaries utilizing normal hypophysectomized, and thyroidless tadpoles Allen[13] clearly demonstrated that the anterior lobe of the pituitary was the portion of the gland concerned with tadpole maturation and that this influence occurred solely through the effect of the pituitary on the thyroid

The dependence of thyroid growth and activity upon normal pituitary function has been observed in amphibia birds and mammals in numerous experiments which are reviewed by Van Dyke[14] Following the demonstration of thyroid hypofunction subsequent to hypophysectomy Smith and Smith[15] showed that the injection of extracts of fresh hypophyses would counteract this decreased function indeed in the normal animal such injections increased thyroid weight and thyroid activity, as measured by increased height of the follicular epithelium in the thyroids of axolotl larvae[16, 1] These experiments led Uhlenhuth and Schwartzbach[16, 17] to postulate the existence of a substance in the anterior pituitary that would cause an increase in thyroid gland activity and in thyroid hormone output Finally in 1930 Crew and Wiesner[18] again using axolotl larvae concluded that extracts of the anterior pituitary contained an activator of the thyroid which was distinct from the growth and gonadotrophic hormones and to which they applied the term thyreotropic hormone

The alterations in thyroid structure and function following hypophysectomy manifest themselves by decreased organ weight and involutional changes characterized by low follicular epithelium and an abundance of deeply staining colloid[19, 20] Parallel with these anatomical changes there occurs evidence of depressed thyroid function The metabolism drops to hypothyroid levels[1] and the blood iodine is similarly decreased However complete myxedema does not develop in animals who have been hypophysectomized or in patients with panhypopituitarism Hypophysectomy depresses but does not completely abolish thyroid function Thus hypophysectomy in the rat does not interfere with conversion of iodide to diiodotyrosine, though there is limitation of the overall conversion of iodide to thyroxine[3] Analyses of rat s gland under these circumstances has shown the presence of normal or even greater than normal amounts of thyroxine in spite of a 50

per cent lowering of the level of hormonal iodine in the blood This finding led Taurog Chaikoff and Bennett [4] to conclude that a lowered concentration of blood thyroxine does not stimulate the thyroid gland into release of stored hormones even when they are present in abundance this release depending upon the action of thyrotrophin Similarly in dogs Bauman Metzger and Marine have shown abundant storage of thyroxine in the form of colloid in the thyroid of hypophysectomized dogs

Hypophysectomy therefore produces a resting colloid rich thyroid histologically and physiologically inactive containing adequate hormone which is not released in normal amounts colloid storage is normal, hormone release is limited or suppressed

The pronounced effects of hypophysectomy upon the thyroid led to a study of the results of transplantation and of the injection of anterior pituitary extracts into animals under various conditions Loeb and Basser [6] and Aron [7] observed that the injection of anterior lobe extracts produced increased cell height in the follicular epithelium of the thyroid of normal animals thus indicating stimulation of thyroidal activity Grant [8] utilizing implants of the anterior pituitary of frogs into amblystoma larvae was able to demonstrate release of the follicular colloid for transcellular migration into the general circulation with eventual complete emptying of the follicles By injection of anterior pituitary powder in the dog Loeser [9] similarly demonstrated depletion of colloid This was associated with increased follicular cell height and papillary infoldings of follicular epithelium such as is seen in thyrotoxicosis

Many other workers have confirmed these results Okkels [3] found an increase in the Golgi apparatus and in the mitochondria following anterior pituitary injections Hertz and Kranes [31] by repeated injections of anterior pituitary extracts in rabbits produced initial thyroid hyperplasia and eventually an involuted gland with atrophy of the epithelium and marked colloid storage Williams [3] observed in living thyroid follicles an increase in the rate and extent of colloid release as a result of injection of anterior pituitary extracts

In man effects similar to complete hypophysectomy were first observed in 1914 by Simmonds [33] who described a clinical syndrome characterized primarily by cachexia with an associated partial failure of thyroid adrenal and gonadal functions this syndrome is now called Simmonds disease In these instances the pituitary has been found atrophic and cicatrized Generalized visceral atrophy also occurs The histology of the thyroid in Simmonds disease varies somewhat but is

to prevent normal metamorphosis by causing thyroid atrophy Subsequently Smith[11] and, independently, Allen[1] found that extirpation of the pituitary anlage in tadpoles caused failure of the thyroid to develop normally with secondary arrest of maturation unless thyroid was administered By transplantation experiments with adult pituitaries utilizing normal hypophysectomized and thyroidless tadpoles Allen[13] clearly demonstrated that the anterior lobe of the pituitary was the portion of the gland concerned with tadpole maturation and that this influence occurred solely through the effect of the pituitary on the thyroid

The dependence of thyroid growth and activity upon normal pituitary function has been observed in amphibia birds and mammals in numerous experiments which are reviewed by Van Dyke[14] Following the demonstration of thyroid hypofunction subsequent to hypophysectomy, Smith and Smith[15] showed that the injection of extracts of fresh hypophyses would counteract this decreased function indeed in the normal animal such injections increased thyroid weight and thyroid activity as measured by increased height of the follicular epithelium in the thyroids of axolotl larvae[16, 1] These experiments led Uhlenhuth and Schwartzbach[16, 17] to postulate the existence of a substance in the anterior pituitary that would cause an increase in thyroid gland activity and in thyroid hormone output Finally in 1930, Crew and Wiesner[18] again using axolotl larvae concluded that extracts of the anterior pituitary contained an activator of the thyroid which was distinct from the growth and gonadotrophic hormones and to which they applied the term thyreotropic hormone

The alterations in thyroid structure and function following hypophysectomy manifest themselves by decreased organ weight and involutional changes characterized by low follicular epithelium and an abundance of deeply staining colloid[19, 0] Parallel with these anatomical changes there occurs evidence of depressed thyroid function The metabolism drops to hypothyroid levels[1] and the blood iodine is similarly decreased However complete myxedema does not develop in animals who have been hypophysectomized or in patients with panhypopituitarism Hypophysectomy depresses, but does not completely abolish thyroid function Thus hypophysectomy in the rat does not interfere with conversion of iodide to diiodotyrosine, though there is limitation of the overall conversion of iodide to thyroxine[3] Analyses of rat s gland under these circumstances has shown the presence of normal or even greater than normal amounts of thyroxine in spite of a 50

latter substance inhibits a similar synthesis within the gland itself Interestingly thiourea administered by itself will not result in extensive degranulation but iodide plus thiourea produces degranulation similar to that following thyroidectomy presumably through synergistic depression of thyroxine synthesis by the thyroid itself [4]

The restoration of granulation by thyroxine or iodide however is not as effective if their administration is delayed too long after thyroidectomy Similarly Severinghaus [46] has shown that in rats thyroidectomized at birth irreversible changes occur in the pituitary there is a permanent absence of acidophil and basophil cells

The rat is unique in the clarity with which a particular cell type can be related to the elaboration of thyrotrophin In the cockerel data are not conclusive and suggest if anything that acidophils are the likely source of thyrotrophin [4] The guinea pig is also different in that no obvious counterpart to the thyroidectomy cells of the rat appears after profound depression of the thyroid D Angelo [4 b] however on the basis of thyrotrophin assays of the blood and pituitary in this animal concludes that thyrotrophin is produced by the basophils

Thyrotrophin

The Thyrotrophic Hormone The unitary nature of the thyrotrophic hormone as it affects the structure and function of the thyroid has not yet been clearly established nor is there always a regularly demonstrable parallelism between the degree of morphological change and functional alteration Heyl and Laqueur [47] found that various pituitary extracts selectively increased thyroid weight or produced hyperplasia Billingsley [48] also concluded that thyrotrophin might have dual effects — one influencing the secretion of the thyroid hormone the other acting upon the gland structure Chemically however the hormone has been characterized as a protein relatively low in molecular weight and probably containing a carbohydrate grouping [49] Though it has not yet been isolated as a pure substance simple procedures for its preparation in highly purified form are now available [6] Previous conclusions about the nature of the hormone may well have been confused by the presence of contaminating materials particularly gonadotrophic substances which are difficult to separate from thyrotrophin Prolactin and the growth hormones are more readily separable

The effects of thyrotrophin on thyroid morphology consist of an increase in the height of the follicular cells hypertrophy and hyperplasia

always consistent with marked hypofunction Means and his associates[34] found a slightly fibrosed small gland containing sparse follicles with low epithelium and little colloid Farquharson[3] also found a small thyroid with great reduction in the number of follicles and extremely thin cells in most cases but in one instance he noted a picture suggestive of early primary myxedema with small irregular bunches of follicles and marked fibrosis

On the other hand, hyperpituitarism as exemplified in man by acromegaly and gigantism is usually associated with marked enlargement of the thyroid gland Changes in the thyroid have been described by Cushing and Davidoff[36] and by Atkinson[37] and are essentially those of colloid hypertrophy frequently with adenomatous formation Elevation of the basal metabolic rate is not uncommon,[38] but instances of true hyperthyroidism rarely occur

The production of hypophyseal enlargement by thyroidectomy occurs through unknown neural mechanisms according to Salter[1] but is associated with increased concentration of thyrotrophin in the blood Zeckwer[39] found large amounts of thyrotrophin in the pituitaries of cretinous rats The histological changes occurring in the anterior pituitary following thyroidectomy in man are characterized by an increase in the number, size, and degree of vacuolization of the basophilic cells and a decrease in the number and size of the eosinophilic cells[40] In rats, inhibition of thyroid function by antithyroidal goitrogens such as Brassica seed and soy bean diets[41, 42, 43] leads to similar changes associated with a definite reduction in the thyrotrophin concentration in the anterior pituitary

Thyroidectomy in rats results in striking changes in both types of chromaffin cells of the pituitary The basophil ('thyroidectomy') cells are greatly increased in number and size while the acidophil or eosinophil cells lose their acidophilic granules and come to resemble the chromophobe cells The degranulation of the acidophil cells occurs only with extreme thyroxine deficiency while the hypertrophy of the basophil cells occurs only in states coinciding with increased production of thyrotrophin Thus Griesbach and Purves[44] have concluded that the basophil cells are the source of thyrotrophin Acidophilic degranulation can be quantitatively prevented by thyroxine administration in amounts as little as 0.25 micrograms per 100 grams of rat daily and has been found a sensitive indicator of the presence of thyroxine in vivo Iodide as well as thyroxine will prevent acidophilic degranulation following thyroidectomy, and this protective action has been ascribed to extrathyroidal thyroxine synthesis This synthesis is inhibited by thiourea just as the

The direct effect of thyrotrophin on the thyroid gland has been assayed by measuring the increase in thyroid weight in acinar cell height, or in the intracellular colloid droplets. It has also been assayed chemically by determining the decrease in thyroid iodine content.

Borrell[61] and Griesbach and Purves[6] have found a specific parallelism between thyrotrophin stimulation and increased cell height in the thyroid of young guinea pigs. The findings of Rowlands and Parks[6] that thyrotrophin quantitatively increases the thyroid weight of the newly hatched chick have been confirmed by Smelser[63] and Adams[64]; this increased weight may be used as a sensitive and reliable method of thyrotrophin assay. DeRobertis[6] and later Dvoskin[67] have described and utilized as an assay method the production of intracellular colloid droplets following thyrotrophin stimulation. This method is sensitive and permits quantitation in as little as 2.0 cc. of human blood but its specificity is open to question since these droplets can form in vitro in the absence of added thyrotrophin.

The assay of thyrotrophin by measurement of the decrease in thyroid iodine content in young cockerels as proposed by Piotrowski and his associates[6b] requires careful selection of animals and season of the year as well as measurement of total iodine content of the thyroid gland to produce assays with a standard error of 25 per cent.

The method of Junkmann and Schoeller[66] has gained the widest acceptance for measuring thyrotrophin activity in units. A unit of activity is defined as that amount of hormone which when injected daily for three days causes recognizable hypertrophy of the epithelium and disappearance of colloid in the thyroids of guinea pigs weighing 100 to 150 grams (Fig. 9–15).

The assay of thyrotrophin in patients with disorders of the thyroid has been attempted by many investigators. It has been particularly studied in Simmonds' disease,[1] acromegaly,[68] myxedema and hyperthyroidism[67, 69, 0, 71, 7, 3]—both in the urine and in the blood. Most of these studies have yielded contradictory data because the assay methods utilized have varied and have not been adequate. Thyrotrophin as it occurs in the hypophysis has not been conclusively demonstrated in the blood and urine of human subjects in spite of the fact that thyrotrophin added in tracer amounts can be satisfactorily recovered from these media by chemical methods.[74]

D'Angelo and his co-workers[74] have investigated thyrotrophic activity in the blood of patients suffering from a variety of endocrine disorders. They have used the starved tadpole for bioassay of thyro-

of the epithelium such as is seen in exophthalmic goiter, vacuolization and eventual resorption of the colloid, and increase in vascularity and gland size [51] [1] Papillary infoldings of the epithelium with colloid absorption have been demonstrated as early as 2 hours after intraperitoneal injection of thyrotrophin into guinea pigs By the end of 24 hours the colloid space has been found decreased by 50 per cent These changes are reversible with complete return to the normal picture 7 days after injections of thyrotrophin have been discontinued [51] On the other hand Loeser [3] and Elmer [54] by continuous and increasing doses of thyrotrophin produced chronic thyrotoxicosis which was eventually fatal

Chemically, thyrotrophin has important effects on the hormonal and iodine content of the thyroid gland and of the blood Following thyrotrophin stimulation the thyroid shows a striking decrease in iodine content [3, 55] especially in the thyroxine like fraction [6, 7] while the hormonal iodine concentration in the blood increases This is analogous to the situation occurring in clinical thyrotoxicosis — low hormonal iodine content of the gland with elevated levels of hormonal iodine in the blood Thyrotrophin not only increases the level of hormonal iodine in the blood but according to Chaikoff and his associates [60] it also greatly augments the rate of conversion of inorganic iodine into the protein bound iodine of the blood In addition as previously indicated with regard to the effects of hypophysectomy [4] the rate at which thyroid hormone is released into the circulation is also controlled by thyrotrophin Closs Loeb and Mackay [58] have shown that thyrotrophic stimulation may reduce the iodine content of the thyroid by over 90 per cent producing a gland that has scarcely any pharmacological activity and only traces of thyroxine

Thyrotrophin is thus seen as the indispensable factor that controls the rate and amount of thyroid hormone production and its release by the gland secondarily it has important effects on blood iodine levels

Assay of Thyrotrophin Thyrotrophin has been assayed both by measuring the secondary effects resulting from the increased activity of the thyrotrophin stimulated thyroid gland and by quantitating its direct effect on the histology and secretory activity of the thyroid Animal species of appropriate sensitivity must be utilized and for this purpose the tadpole guinea pig or chick have been found most responsive The metamorphosis of amphibian larvae such as the tadpole has largely served as the basis for measurement of the indirect effect of the thyroid gland stimulated by thyrotrophin [63] The tadpole possesses the advantages of convenience and sensitivity but its specificity is not as clearly established as that of the guinea pig and chick

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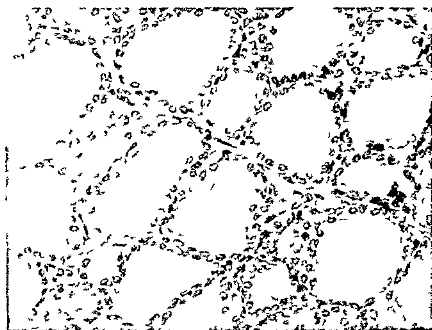


Fig 9 Thyroidea from guinea pig Normal animal Cell height $8 3 \pm 0 15 \mu$ The follicles well filled with colloid Few vacuoles



Fig 10 Thyroidea from guinea pig Normal animal Clear border line between follicle cells and colloid

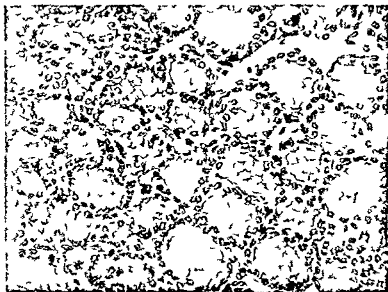


Fig 11 Thyroidea from guinea pig killed hours after a single injection of MsF of thyrotropic hormone Cell height 8 8 ± 0 11 μ Great vacuolization of the colloid

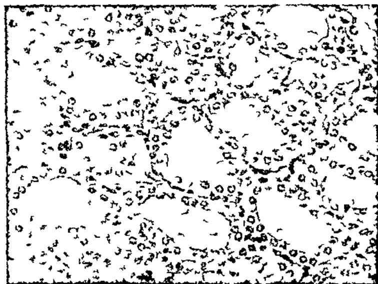


Fig 12 Thyroidea from guinea pig killed 12 hours after a single injection of 2 MsF of thyrotropic hormone Cell height 10 2 ± 0 10 μ

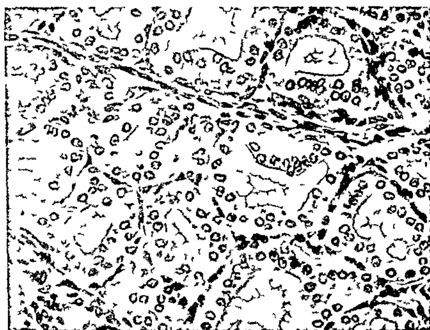


Fig 13 Thyroidea from guinea pig Killed after 4 daily injections of 2 MsE of thyrotropic hormone Cell height 14 1 ± 0 14 μ In places the follicle walls bulge into the lumen The nuclei are localized in parts of the cell which are directed toward the lumen

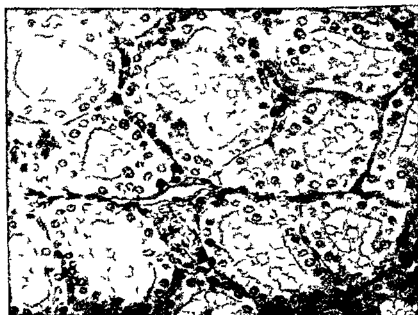


Fig 14 Thyroidea from guinea pig Killed after 8 daily injections of 2 MsE of thyrotropic hormone Cell height 14 4 ± 0 12 μ Great vacuolization of the colloid



Fig 15 Thyroidea from guinea pig which received 2 MsL of thyrotropic hormone daily during 8 days Some of the follicle cells cut very obliquely All illustrations in this section are from Borell U On the transport route of the thyrotropic hormone the occurrence of the latter in different parts of the brain and its effect on the thyroidea Acta Med Scand 1945 Supplement clxi 1 2 7

trophin since complete starvation induces thyroid atrophy and meta morphic stasis in this animal This method is sensitive enough to measure the presumably low concentrations of thyrotrophin in human body fluids The studies of this group indicate that there is probably an increase in thyrotrophin in hyperpituitarism and a decrease in hypo pituitarism *The great majority of hypothyroid individuals did not show* excessive titers of thyrotrophin conversely in hyperthyroidism thyro trophin levels were usually normal D Angelo and his associates there fore postulate that the hyperplasia and increased activity of the thyroid gland in thyrotoxicosis cannot be attributed to an abnormal concentra tion of thyrotrophin in the blood In addition they found ophthalmo pathic hyperthyroidism present when thyrotrophin was either absent normal or excessively high high levels found in acromegaly and in occasional cases of primary myxedema were not associated with exophthalmos

Thyrotrophin Iodine and Thyroid Hormone Early investigations by Loeb and his co workers[7, 78] demonstrated that the administration of thyroid substance partially inhibited the thyroid hyperplasia caused by

thyrotrophin. This finding was confirmed for thyroxine by Aron and his associates[77] and by Loeser and Thompson.[78, 79] The latter investigators also found, as had Kuschinsky[80] before them, that large doses of iodine led to increased thyrotrophin content of the pituitary, whereas small doses depressed its production.

Kuschinsky[80] clearly showed the equilibratory relations between the thyroid hormone and thyrotrophin by assaying in guinea pigs the pituitary glands of rats that had received thyroxine. The cellular hyperplasia *of the thyroid produced by the implantation of pituitaries from* normal rats failed to occur when pituitaries from thyroxinized rats were used. Adams and Jensen[81] found a 90 per cent decrease in the thyrotrophic content of anterior pituitaries of thyroxinized mice. Cortell and Rawson[82] observed that thyroxine depressed the response of the animal's thyroid gland to thyrotrophin both in normal and in hypophysectomized animals. More recently Purves and Griesbach,[83] utilizing the same method as Kuschinsky,[80] concluded that thyroid administration depressed the thyrotrophic activity of the rat's pituitary by over 95 per cent. In an over-all application of this work as well as of his own research Marine[84] concluded that in the normal animal thyrotrophin is the sole cause of increased thyroidal activity, and that inadequate supply of environmental iodine leads to goiter through thyrotrophic stimulation of the thyroid.

The effect of iodine upon the reciprocal relation between the pituitary *and the thyroid has been studied in the living organism,* in tissue slices and in the test tube. Siebert and Thurston,[85] Friedgood,[86] and Elmer[4] all found that iodides inhibited an established thyrotrophic effect. Anderson and Evans found that potassium iodide inhibited the metabolic effect of thyrotrophin without interfering with the changes in the thyroid itself, possibly accomplishing this effect by preventing the discharge of thyroxine from the gland.

In vitro experiments by Seidlin[88] have suggested that thyroid tissue in some way inactivated or removed thyrotrophic hormones from surrounding solutions. Galli Mainini[89] similarly found an in vitro inhibition of thyrotrophin when it was placed in contact with thyroglobulin. Rawson and his co-workers[90] likewise observed that normal thyroid tissue removed the thyrotrophic effect of pituitary extracts, and again that thyroid slices from thyrotoxic patients inactivated twice as much thyrotrophin as normal thyroid.[91] Finally Albert, Rawson and Merrill[92] added elemental iodine to pituitary extract in the test tube and abolished thyrotrophic activity in proportion to the amount of iodine added; with enough iodine most of the thyrotrophin was inactivated. Junqueira[93]

has reported a similar inhibition of thyrotrophin by iodide added to thyroid fragments in vitro

Metabolic Effect of Thyrotrophin The marked histological changes produced in the thyroid gland by thyrotrophin are indicative of increased secretion of thyroid hormone This in fact is borne out by studies on experimental animals Siebert and Smith[94] Anderson and Collip[2] and others[96] have shown that thyrotrophin elevates the metabolic rate for about 2 weeks and that after this period there ensues a return to normal or depressed values unless increased amounts of thyrotrophin are administered[3,4] This metabolic effect does not occur in the absence of the thyroid gland[97,98] The hypermetabolism is correlated with decreased thyroxine iodine content of the gland and marked increase in organically bound blood iodine suggesting that the rise in oxygen consumption is due to release of increased amounts of thyroid hormone[19]

The transient effects of moderate doses of thyrotrophin upon the thyroid histology and metabolic rate led Collip[11] to investigate the possible existence of anti hormones as an explanation of the refractory state Whether anti hormones as such develop or whether the phenomenon may be explained on the basis of antibodies developed to react against the protein portion of thyrotrophin as suggested by Werner[101] is at present unsettled Since large doses will produce permanently hyper throid states the explanation of this relative refractoriness may be of the nature of tachyphylaxis — i e the development of tolerance to repeated administration such as is seen with other drugs and biological agents

Measurement of the oxygen consumption of thyroid tissue itself has been utilized in further studies of the physiological effects of thyrotrophin The technique of Warburg for measurement of tissue oxygen consumption (QO_2) has been utilized by some investigators The metabolism of thyroid slices from animals previously injected with thyrotrophin or the addition of thyrotrophin to the medium in which thyroid slices from normal untreated animals are suspended have provided alternative approaches to this study Paal[1] Canzanelli and Rapport[103] and VanderLaan and his co workers[104] have utilized the former technique whereas Anderson and Alt[105] and Galli Mainini[6] have used normal thyroids bathed in a thyrotrophic containing medium In both groups of experiments the oxygen consumption was found increased but this increase was greater in the pre treated animals Borell[93] has carefully reviewed and restudied the findings in the thyrotrophin treated animal and has clearly shown that within several hours after such

thyrotrophin. This finding was confirmed for thyroxine by Aron and his associates[7] and by Loeser and Thompson.[78, 79] The latter investigators also found, as had Kuschinsky[80] before them, that large doses of iodine led to increased thyrotrophin content of the pituitary, whereas small doses depressed its production.

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euthyroid hyperthyroid or acromegalic They observed maximum effects from thyrotrophin during the first 24 hours in thyrotoxic patients and not until 48 hours later in euthyroid subjects

Thyrotrophin and Exophthalmos

Thyrotrophin is significantly related to the production of exophthalmos in the experimental animal Gley[138] first noticed the occurrence of exophthalmos following thyroidectomy in young rabbits Zimmerman[164] *similarly noted exophthalmos following thyroidectomy in* patients with hyperthyroidism Loeb and Bassett[8] Schockaert[110, 111] and Loeb and Friedman[11] first demonstrated that exophthalmos frequently ensued following injection of anterior pituitary extracts in guinea pigs and ducks Schockaert for instance found that 14 out of 15 ducks injected with a crude extract of the anterior hypophysis developed exophthalmos after 3 weeks of treatment

Marine and his associates[113, 114, 115] *later discovered that the goitrogen* methyl cyanide frequently produced exophthalmos in rabbits that this exophthalmos was proportional to goitrogenesis that it did not occur in resistant rabbits which failed to develop thyroid hyperplasia and that this resistance could be completely abolished by thyroidectomy Thyroidectomy in fact increased any existing exophthalmos Iodine administration prevented exophthalmos in rabbits with an intact thyroid but administered *thyroid did not abolish an existent exophthalmos Marine felt that* cyanide produced thyroid hyperplasia by stimulation of the anterior pituitary and then demonstrated that extracts of this gland would produce *exophthalmos in normal and in thyroidectomized guinea pigs in* the former group no exophthalmos developed until the thyroid became hyperplastic Furthermore Marine[116, 117] found that castration inhibited the exophthalmos produced by the anterior pituitary while testosterone accelerated its appearance

Smelser[118, 119, 120, 121] has elucidated the subject further He found that injections of anterior pituitary extracts produced hyperfunctioning goiters *in guinea pigs but no significant exophthalmos except in thyroidec*tomized guinea pigs Under these conditions marked exophthalmos developed after 2 to 3 weeks of treatment The development of this exoph*thalmos was not prevented by excision of the cervical sympathetic gang*lion and persisted after death The orbital contents in these animals were increased in weight and size primarily because of an increase in the

treatment the removed thyroid will have an elevated QO_2 or oxygen consumption which will be maintained under the influence of daily injections for about 7 weeks when a great decline occurs with the development of very low values for QO_2.

Another important metabolic effect of thyrotrophin is alteration of the glycogen content of the liver. Continued injections of thyrotrophin will entirely deplete the liver of its glycogen,[105] provided the thyroid gland is present but will have no effect in thyroidectomized animals. This glycogenolytic effect may, therefore, be viewed as a secondary action of thyrotrophin mediated entirely by the release of thyroxine.

The relation of this physiological and experimental data to clinical states is far from clear. Thompson and his co-workers[106] have been able to elevate transiently the metabolic rate of normal and goitrous patients through the use of extracts of the anterior pituitary and at the same time to produce thyrotoxic symptoms. This work is suggestive but needs confirmation. On the other hand, pathological studies have failed to disclose alterations in the histology of the anterior pituitary in thyrotoxicosis in man.[107]

Though the relation of clinical hyperthyroidism to thyrotrophin is unknown, there has been some clarification of the normal role of thyrotrophin in human thyroid physiology. Many investigators have administered thyrotrophin in a relatively impure form to human subjects in various states of thyroid function, and its effects have been studied by tracer amounts of radioactive iodine. Stanley and Astwood[107a] found a latent period of 8 or more hours before there was a detectable increase in thyroid activity as measured by increased organic binding of iodine by the thyroid and by its increased capacity to concentrate the iodide ion, i.e. iodine uptake. These two processes were demonstrated to be independent since increased uptake or iodine concentrating capacity occurred when organic binding was inhibited by mercaptoimidazole. Goldsmith and his associates[107b] similarly found that in thyrotoxic patients thyrotrophin increased the rate of release of thyroid hormone from the thyroid hormone stores in spite of the inhibition of iodide accumulation in the thyroid by mercaptoimidazole. The total amount of hormone release was naturally smaller in the thyrotoxic gland than in the euthyroid gland since the hyperthyroid gland is already depleted of its hormone stores but the rate of release is made even greater by thyrotrophin. Beckler and his associates[107] also noted that thyrotrophin increased the levels of both protein bound radioactive iodine (PBI^{131}) and ordinary protein bound iodine in the blood of patients who were

depended on the dosage He found no difference between normal and thyroidectomized animals ascribing the differences reported by other observers to the greater weight loss in the intact animal In the animals used in these experiments the exophthalmos was found to be due largely to increased water content of the orbit

Rundle and Pochin [1] also studied the manner and degree of exophthalmos in thyrotoxic patients at post mortem examination By chemical rather than histological techniques they were able to demonstrate that the increased bulk of the orbit which occurs in thyrotoxic patients was mainly due to increased fat content in the orbital structures even in the presence of emaciation

This increase of fat was relatively greatest in the eye muscles particularly in the levator palpebrae superioris though the increase in the general orbital fibro fatty tissue was responsible for most of the increase in bulk Rundle and Pochin s conclusions were based largely on the amount of ether soluble material extracted from these orbits and it is important to point out particularly in view of Smelser s conclusions with histological techniques that no attempt was made to analyze other materials such as collagen or nuclear material which may have increased *pari passu* with the fat

In the guinea pig Smelser [10] found that anterior pituitary exophthalmos was unaffected by the coincident administration of sodium iodide and that thyroxin reduced the incidence of exophthalmos Diiodotyrosine had no effect on the orbital contents in the normal or exophthalmic pigs whereas thyroxine caused a marked enophthalmos by reducing the contents of the orbit Exophthalmos however could be produced in hyperthyroid pigs but in lesser degree than in thyroidectomized animals

Albert [16] has investigated the problem in *Fundulus* the common Atlantic minnow In this fish striking proptosis was regularly produced by injection of adequate amounts of anterior pituitary extracts The active principle of these extracts was shown to be closely associated with thyrotrophin since all preparations that induced exophthalmos also produced thyroid hyperplasia in hypophysectomized frogs and turtles conversely anterior pituitary preparations that did not produce exophthalmos had no thyroid stimulating action Albert labeled this fraction the exophthalmic factor and further noted that exophthalmos preceded thyroid hypertrophy and hyperplasia by at least 1 hours The mechanism of the exophthalmos in *Fundulus* consisted of increased intra orbital pressure due to free retrobulbar fluid and edema of the areolar and fat tissue within the orbit This investigator is critical of the general belief that

fatty connective tissue the dorsal lacrimal gland, and the extra ocular muscles The retrobulbar tissues contained a stainable infiltrate showing granules droplets — probably lipoid in nature — and round cells penetrating between the fat cells and into the connective tissue The extra ocular muscles showed irregular clumps of round cells and the same type of edematous infiltration as was seen in the retrobulbar tissues In addition the orbital tissues showed considerable numbers of wandering cells

Paulson[1] confirmed many of Smelser's observations finding however that exophthalmos developed readily in guinea pigs with intact thyroid glands although not in every animal and never to the same degree as in the thyroidectomized pig The orbital tissues of these animals contained excessive water in the fat connective tissues and muscles, as well as cellular infiltration

Dobyns[1,3] has correlated the orbital changes caused by thyrotrophin with generalized tissue changes He too found that the development of exophthalmos was facilitated by thyroidectomy but that exophthalmos was induced readily in animals with intact thyroid glands when they were given adequate doses of thyrotrophin He observed large numbers of mononuclear and polymorphonuclear cells in the connective tissue throughout the body following thyrotrophin injection With these cells were associated varying edema and fibroblastic proliferation The fat depots including the orbit of the animal showed many phagocytic cells both polymorphonuclear and mononuclear, along with fibroblasts containing tiny fat droplets Dobyns inferred that the macrophages turned into fibroblasts which in turn laid down connective tissue There was edema in the interstices of the connective tissue and in the orbital fat as well as separation of the muscle fibers apparently by edema fluid

Smelser[115] has compared the orbital changes of patients dying with thyrotoxicosis with what has been found in exophthalmos produced experimentally by injections of anterior pituitary extract In man he found an edematous infiltrate and wandering cells in the fat connective tissue, and muscles The infiltrate was seen as a stainable substance which penetrated between the collagen fibers of the connective tissues and at times between the fat cells, resembling closely the material found in the guinea pigs The wandering cells appeared as in the guinea pigs, and the muscle changes were also similar consisting of edema and round cell infiltration

Pochin[1,4] utilizing objective ocular measurements demonstrated that exophthalmos could be produced readily in growing guinea pigs by injection of anterior pituitary extract and that the degree of exophthalmos

depended on the dosage He found no difference between normal and thyroidectomized animals ascribing the differences reported by other observers to the greater weight loss in the intact animal In the animals used in these experiments the exophthalmos was found to be due largely to increased water content of the orbit

Rundle and Pochin[1] also studied the manner and degree of exophthalmos in thyrotoxic patients at post mortem examination By chemical rather than histological techniques they were able to demonstrate that the increased bulk of the orbit which occurs in thyrotoxic patients was mainly due to increased fat content in the orbital structures even in the presence of emaciation

This increase of fat was relatively greatest in the eye muscles particularly in the levator palpebrae superioris though the increase in the general orbital fibro fatty tissue was responsible for most of the increase in bulk Rundle and Pochin s conclusions were based largely on the amount of ether soluble material extracted from these orbits and it is important to point out particularly in view of Smelser s conclusions with histological techniques that no attempt was made to analyze other materials such as collagen or nuclear material which may have increased *pari passu* with the fat

In the guinea pig Smelser[10] found that anterior pituitary exophthalmos was unaffected by the coincident administration of sodium iodide and that thyroxin reduced the incidence of exophthalmos Diiodotyrosine had no effect on the orbital contents in the normal or exophthalmic pigs whereas thyroxine caused a marked enophthalmos by reducing the contents of the orbit Exophthalmos however could be produced in hyperthyroid pigs but in lesser degree than in thyroidectomized animals

Albert[16] has investigated the problem in *Fundulus* the common Atlantic minnow In this fish striking proptosis was regularly produced by injection of adequate amounts of anterior pituitary extracts The active principle of these extracts was shown to be closely associated with thyrotrophin since all preparations that induced exophthalmos also produced thyroid hyperplasia in hypophysectomized frogs and turtles conversely anterior pituitary preparations that did not produce exophthalmos had no thyroid stimulating action Albert labeled this fraction the exophthalmic factor and further noted that exophthalmos preceded thyroid hypertrophy and hyperplasia by at least 12 hours The mechanism of the exophthalmos in *Fundulus* consisted of increased intra orbital pressure due to free retrobulbar fluid and edema of the areolar and fat tissue within the orbit This investigator is critical of the general belief that

thyrotrophin causes exophthalmos because of the relative impurity of the extracts thus far employed by others He points out that his own work has shown an intimate relation between thyrotrophin and the exophthalmic factor since both are located in the same mixture of pituitary proteins and may prove to be identical Dobyns and Steelman,[126] however, after studying a variety of pituitary extracts, were able to separate an exophthalmos producing substance from thyrotrophin, utilizing the production of exophthalmos in the *Fundulus* as an assay method Their separations were fairly complete in that all of the exophthalmogenic factor could be removed from thyrotrophin, and most of the thyrotrophin could be removed from the exophthalmos producing factor

The Regulation of Thyrotrophic Activity

Thyrotrophin acts directly on the thyroid cell through a humoral mechanism which does not require the mediation of nervous tissue as was first shown in vitro by Eitel Krebs, and Loeser[127] Marine and Rosen[128] similarly demonstrated stimulation of thyroid transplants by thyrotrophin Krayer[129] Uotila[130] and Loewe, Ivy, and Brock[131] have conclusively shown that the cervical sympathetic chain is not essential for the effect thyrotrophin has on the thyroid Uotila[132] has further shown that the reciprocal relation between thyroxine and thyrotrophin is independent of hypothalamic stimuli passing through the pituitary stalk The anterior pituitary of animals shows similar changes following thyroxine administration whether the stalk is intact or partially or completely transected Thyrotrophic function is basically regulated by variations in the thyroxine level of the blood Cervical sympathectomy may have a minor and temporary role in decreasing thyrotrophic function, but no permanent effect ensues Similarly under the stress of cold the pituitary stalk may transmit stimuli from the hypothalamus with modification of the thyroxine thyrotrophin balance Jacobsohn and Westman[133] have contrasted the relative independence from the hypothalamus of thyrotrophin with the dependence of the gonadotrophic hormone upon the hypophyseal-hypothalamic relationship

Greer[133a] however, on the basis of carefully placed electrolytic lesions in the hypothalamus of rats and of intra-ocular transplantation of the pituitary in hypophysectomized mice, has suggested that thyrotrophin consists of at least two factors—a 'growth' factor and a 'metabolic' factor The growth factor regulates thyroid cell height and gros s

thyroid size and depends on the integrity of certain areas of the hypothalamus which have some manner of direct communication with the anterior pituitary The metabolic factor is independent of the hypothalamus enabling the thyroid to concentrate and bind iodine

It is entirely probable that thyrotrophin can pass directly into the blood stream Westman and Jacobsohn[134] have demonstrated this likelihood with regard to gonadotrophin Borell[61] has concluded that the thyrotrophic hormone is transported by way of the stalk of the hypophysis to the tuber cinereum whence it reaches the choroid plexus probably by way of the third ventricle Alternate routes of transport undoubtedly exist

The Interrelation of the Thyroid and the Neuro hypophysis

The role of the thyroid hormone in water exchange has been discussed in Part I The production of diuresis in normal animals by the administration of anterior hypophyseal extracts containing thyrotrophin led several investigators[11 136] to conclude that the diuretic action of the anterior hypophysis was mediated through the thyroid gland In an extensive and meticulous series of investigations on the neuro hormonal control of water balance Fisher Ingram and Ranson[137] restudied this problem in cats with experimental diabetes insipidus They found a variable effect from thyroidectomy some animals developed a 50 per cent reduction in the level of fluid exchange though others showed no appreciable reduction but in no case did the water exchange fall to normal *The administration of thyroid extract in doses of 1 gram daily* restored the fluid exchange to its level before thyroidectomy

These authors also studied the effect of thyroid administration on normal cats and on cats with diabetes insipidus The dosage of thyroid used was very large varying from 1 to 4 grams daily Very little increase in water exchange occurred even after unphysiological doses over a period of several weeks In the cats with diabetes insipidus there was marked increase in the fluid exchange with doses of thyroid that had little effect on the normal animals The greater sensitivity to thyroid was ascribed to a deficiency of the antidiuretic hormone of the neuro hypophysis with exaggeration of the diuretic tendency by the administration of thyroid

Hembecker and his associates[13] have clarified further the role of the thyroid in diabetes insipidus by showing that in dogs the pars distalis

of the anterior hypophysis must be left intact to produce permanent maximal diabetes insipidus following the destruction or denervation of the neuro hypophysis Removal of the pars distalis shortens and ameliorates the extent of the diabetes insipidus by causing secondary atrophy of the thyroid and adrenal cortex with abolition of their diuretic activity Their work suggests the possibility that thyrotrophin is elaborated in the pars distalis of the anterior pituitary

Total thyroidectomy has been utilized in human cases of diabetes insipidus with variable results Findley and Heinbecker [139] and Ferro Luzzi [140] found no improvement following the operation, whereas Blotner and Cutler [141] observed great improvement in 2 out of 3 patients who were subjected to total thyroidectomy

Thyroid-Parathyroid Interrelations

There is little or no evidence indicating any direct relation between the thyroid and parathyroid glands in the endocrine system of normal individuals The relative roles of these two glands in the regulation of mineral metabolism has been discussed in Part I Various authors however have found a parallelism in the response of the thyroid and parathyroid glands to various hormones Zondek [14] has shown that there is simultaneous stimulation of the thyrotrophic and parathyrotrophic functions of the pituitary by prolonged injections of estrogen Nathanson and his associates [143] found that injections of testosterone propionate in rats increased the proliferative activity of the thyroid and parathyroid glands They ascribed this action to stimulation of the anterior hypophysis Finally Blumenthal and Loeb [144] have noted that administration of anterior hypophyseal extracts caused increased mitotic activity and cell proliferation in both the thyroid and parathyroid glands and that underfeeding as well as the administration of thyroid substance resulted in a marked decrease in mitotic activity in both the thyroid and parathyroid glands The cause of this parallel response remains unexplained particularly in view of the disputed existence of a parathyrotrophic hormone

Interrelations of the Thyroid and Adrenals

Though it appears that the thyroid and adrenals have a significant relationship the exact endocrine balance and the mechanisms involved have not been clarified Marine has maintained that an antagonistic rela-

tion exists between the two glands he bases his view on the finding of *increased metabolism following bilateral adrenalectomy and on the persistent* elevation of metabolism that follows sublethal injury to the adrenals[14, 146] The effect of adrenalectomy in raising the metabolism of experimental animals has been confirmed by Davis and Hastings[147] It must be that the increased metabolism following reduced function of *the adrenal cortex is mediated through the thyroid gland for it does* not occur in athyreotic animals[14] Adrenal hypertrophy frequently occurs in hyperthyroidism[149] and the administration of thyroid produces adrenal cortical enlargement[13, 150] On the other hand Bock[151] found that adrenal cortical extract behaves synergistically with thyroxin in the acceleration of tadpole and axolotl metamorphosis

Baumann and Marine[7] in more recent studies produced involution of the adrenal cortex in rats by thiouracil ingestion and considered this regression as a compensatory reaction to loss of thyroid secretion The action of the thyroid in causing adrenal cortical hypertrophy is mediated through the hypophysis since thyroxin will not induce hypertrophy of the adrenal cortex in hypophysectomized animals[150, 153, 154] Furthermore thyrotrophin itself will produce adrenal cortical hypertrophy[5, 146] which can be prevented by iodide[17]

The availability of adrenocortical steroids and of corticotrophin has restimulated interest in the relations between the thyroid and the adrenal glands This relationship has been investigated in both man and experimental animals by determining the effect of cortisone or corticotrophin representing respectively exogenous and endogenous adrenocortical steroids upon thyroidal metabolism as measured by oxygen consumption levels of protein bound iodine radioactive iodine uptake the renal plasma clearance of radioactive iodine and particularly in animals quantitation of the amount of thyrotrophin in the anterior pituitary or in the blood

Cortisone in doses of 100 mg daily quite regularly inhibits the iodine accumulating function of the thyroid and usually produces an increase in the clearance of I[131] by the renal plasma according to Berson and Yalow[1] This effect of cortisone is persistent so long as adequate amounts are administered but disappears within a few days after its omission The depressed uptake of I[131] represents a true decrease in thyroid function rather than a lessened availability of iodine from increased renal excretion for the thyroidal plasma I[131] clearance was clearly decreased Thus according to these authors the capacity of the thyroid cells to clear plasma of its I[131] content is strikingly diminished by cortisone

Cortisone in daily doses of 400 to 500 mg markedly depresses the uptake of I^{131} in euthyroid individuals and, when the cortisone is given intramuscularly causes a depression that may persist for weeks because of the depot' effect of intramuscularly administered cortisone Concomitantly there is usually a significant decrease in the level of protein bound iodine of the blood and an increase in the serum cholesterol These laboratory signs of thyroidal depression do not occur in patients with thyrotoxicosis who are given massive doses of cortisone, according to Fredrickson Forsham and Thorn [1 b]

The mechanism responsible for the inhibition or depression of I^{131} uptake by adrenocortical steroids is not entirely clear Albert and his co-workers [1] properly point out that thyroid function should be defined as the amount of hormone secreted by the gland in a unit of time that is the hormonal secretion rate This is not a feasible measurement The rate of biologic decay of thyroidal I^{131} however, may be utilized as an indirect measurement of the rate of hormone secretion and as a more sensitive criterion of thyroidal function than I^{131} accumulation Albert [1] found that cortisone and corticotrophin did not depress the I^{131} secretion rate of the rat's thyroid, even though they did depress uptake as in man He concludes therefore that the depressed uptake cannot be due to inhibition of thyrotrophin since both uptake and discharge of I^{131} are strikingly lowered when thyrotrophin is absent or inhibited Halmi and Barker [1 d] indeed found that cortisone administered to rats produced histological evidence in both pituitary and thyroid glands of an increased rate of thyrotrophin release from the pituitary D Angelo and his associates [1] came to similar conclusions Halmi [1 f] in addition has demonstrated that cortisone treated rats have an unimpaired capacity to concentrate iodide despite a defective I^{131} uptake

From the work of Albert and Halmi it may be concluded that cortisone does not inhibit thyrotrophin and does not prevent access of iodide to the thyroid cell Cortisone must therefore depress uptake either (1) by affecting the extrathyroidal metabolism of iodide through increasing renal excretion or iodide space or (2) by partially inhibiting organic binding of iodine in the thyroid Ingbar and Chandler [1 7k] found that the rate of clearance of plasma iodide by the thyroid glands of hypophysectomized rats was unaltered by cortisone even when thyrotrophin was administered The decreased uptake of I^{131} in these animals resulted entirely from a marked increase in the renal clearance of iodide In this regard they found that desoxycorticosterone was antagonistic to cortisone diminishing iodide clearance by the kidneys

In man Zingg and Perry[1] noted that desoxycorticosterone in daily doses of 10 mg for 3 days depressed the uptake of I^{131} as much as cortisone in a dose of 150 to 250 mg daily and that neither affected the renal clearance of iodide The thyroid glands of their patients had a lowered clearance of I^{131} resulting from the administration of both steroids Thus they conclude as did Berson and Yalow[1] that cortisone truly depresses thyroid function

The relation of the thyroid to the adrenal medulla is also unclear Thyrotoxic patients and animals show an increased sensitivity to epinephrin This has served as the basis for the Goetsch test in the diagnosis of hyperthyroidism[1,8] Soffer and his associates[1,9] have found that epinephrin will produce thyroid hyperplasia in dogs evidently through stimulation of thyrotrophin since its causes marked increase in circulating thyrotrophin in thyroidectomized animals

Botkin and Jensen[1] found that epinephrin administered to rats quickly produced a lowered iodine content in the thyroid gland with a decrease in serum iodine concentration whereas thyrotrophin caused an increased serum iodine with a lowered gland iodine Epinephrin possibly exerts its effects on the peripheral tissues thus increasing the demand for thyroid hormone If this is true immediate utilization by the tissues would cause a decrease in serum hormone which would in turn cause a release of pituitary thyrotrophin with restoration of normal blood thyroid hormone levels by increased output from the thyroid gland

Interrelations of the Thyroid Gonads and Breast

Although there is a striking incidence of all types of thyroid disease in the female the relations between the thyroid and the ovary are not at all of the same order of significance as those between thyroid and pituitary

In normal animals and in animals receiving iodides the iodine concentration in the ovary is second to that found in the thyroid itself[1,10,161] The concentration of iodine in the ovary however is less than one fiftieth of the concentration in the thyroid The nature of this iodine has not been determined but it represents no significant amount of thyroxine iodine

During the sexual cycle of the female there is evidence of alteration in the physiological activity of the thyroid Chouke[1,6,163] and his fellow workers have found that the proliferative activity of the thyroid gland

as measured by mitotic changes, is greatest during the first week of the estrus cycle and decreases to a minimum about the tenth day Loeser[164] found increased thyrotrophic production and secretion following ovariectomy in guinea pigs On the other hand thyroidectomy in the rat is followed by a decrease in pituitary gonadotrophic activity[165] This decrease apparently involves chiefly the luteinizing rather than the follicle stimulating hormone according to Chu[166] His animals showed increased numbers of large follicles but no postcoital ovulation as in the normal

The menstrual pattern in hyperthyroidism and myxedema has been studied by Goldsmith and his associates[166a] who utilized endometrial biopsies and pregnanediol excretion as indices of phasic ovarian activity In thyrotoxicosis the predominant menstrual pattern was of oligomenorrhea with occasional amenorrhea The amenorrhea was usually caused by ovulatory failure with hypoestrinism When the menses were scanty or infrequent ovulation continued normally Amelioration of the thyrotoxic state usually resulted in restoration of a normal menstrual pattern even before complete euthyroidism occurred

In premenopausal myxedema, irregular and acyclic bleeding or amenorrhea usually occurred Ovulatory failure was the rule with occasional instances of normal physiologic menstruation Characteristically the myxedematous patient exhibited failure of ovulation with a continuous estrin effect on the endometrium and the development of metropathia hemorrhagica The defect in myxedema would therefore appear to lie in decreased production of the luteinizing hormone by the pituitary or in failure of ovulation despite adequate supplies of hormone The establishment of euthyroidism quickly brought about normal menstrual cycles

Excessive amounts of thyroid in the diet of growing rats has been found to prevent normal ovarian development[167] Conversely, estrogens may lower the iodine content of the thyroid,[168] while ovariectomy is followed by a relative increase in thyroid iodine[169]

In pregnancy marked changes occur in the thyroid There is increased demand for iodine with resultant goiter if the diet is deficient in iodine The blood iodine rises above normal at the third month and reaches a maximum at the seventh month[170] Corresponding with this hyperiodemia is an increased basal metabolic rate, the increased blood iodine probably represents elevated amounts of circulating hormone This hyperiodemia is not transmitted to the fetus[171] Whiteside[172] has reported abortion or fetal death in pregnant rabbits injected with thyrotrophin

and ascribes this effect to excessive thyroxine which has penetrated the placenta[173]

The physiologic rise in the protein bound iodine in human pregnancy[173a, 1 3b] is perhaps due to the increased estrogen production characteristic of pregnancy Engstrom and his co workers[173c] have demonstrated that the serum precipitable iodine rises with estrogen administration often increasing to the levels observed in mild thyrotoxicosis

Sexual activity itself appears to be affected by the thyroid only because of general metabolic changes Thus thyroidectomized male rats display no mating behavior yet the thyroidectomized female is capable of fertile breeding Young[173d] and Petersen[1 3e] and their associates have found that in the guinea pig there is no close relation between the thyroid and reproduction either in the male or female and that there is a wide range of thyroid activity compatible with reproduction Similarly a thyroidectomized bull produces fertile seminal fluid capable of successful artificial insemination[174]

The thyroid gland appears to be essential for mammary development particularly proliferation of the ducts Thus in thyroidectomized cows estrogen will not produce mammary growth unless thyroid is administered[17] Thyroidectomy produces inhibition of duct development in immature male rats but at the same time there is stimulation of alveolar development[1 6] Similarly thyroxine enhances the stimulating effects of progesterone and estrogens upon the growth of lobules and alveolar tissue in mice Thyroidectomy inhibits the ability of these mice to respond to progesterone and estrogen[177] Desiccated thyroid alone will cause duct proliferation and hyperplasia of the end buds in male mice Castrated male mice will not respond in this fashion to thyroid administration[1 8]

Interrelations of the Thyroid and the Pancreas

The relation of the thyroid to carbohydrate metabolism has been discussed in Part I Houssay and his associates[1 9] have extended their studies on this subject particularly with regard to alloxan and pancreatic diabetes in the rat The response in this animal has many remarkable differences from the reaction in the dog or the cat In the latter animal it will be recalled there was little influence on carbohydrate metabolism by thyroxine thyrotrophin or thyroidectomy In the dog on the other hand the administration of thyroid tended to aggravate existing diabetes and in general to have a diabetogenic effect In the rat thyroidectomy coun

teracted somewhat the diabetogenic action of alloxan Thiouracil treatment was even more antagonistic to the action of alloxan Thyroidectomy simultaneous with subtotal pancreatectomy, prevented the appearance of diabetes but as with the dog had no effect on manifest diabetes Thiouracil treatment acted in similar fashion Administration of thyroid to pancreatectomized rats caused premature appearance of diabetes but this type of diabetes disappeared gradually and permanently, despite continuous treatment with thyroid In animals not treated with thyroid permanent diabetes regularly followed pancreatectomy Finally the administration of thyroid to pancreatectomized diabetic rats resulted in complete disappearance of the diabetic state

The relation of these findings in animals to the thyroid and pancreas interplay in the human is certainly unclear Is man like cat, dog or rat The answer to this intriguing question must await more specific methods of study of the hormonal balance involved

Interrelations of the Thyroid and Thymus

Thyroid thymus interrelations are concerned chiefly with growth processes According to Gudernatsch [180] thyroid feeding produces acceleration of metamorphosis and cessation of growth of tadpoles whereas thymus feeding results in acceleration of growth and failure of metamorphosis Speidel [181] noted that the feeding of thyroid to tadpoles causes definite changes in the thymus the lymphocytes of the thymus and elsewhere were stimulated to mitotic proliferation Richter and Wislocki [182] however found hypoplastic thyroids and adrenals with enlarged thymus and lymph nodes in hypophysectomized rats

Sunder Plassmann [183] has described connections between the thyroid and thymus in the newborn consisting of large epithelioid cells with light nuclei which are controlled by the vegetative nervous system This author believes that thyroid secretion is fixed by the lymphocytic cortex of the thymus because he has noted atrophy of the thymus following thyroidectomy and hyperplastic changes in the thymus, when thyroidectomized patients are fed thyroid extracts

Rehn [184, 185] has investigated the function of the thymus in ten cases of exophthalmic goiter utilizing the method of Bomskov [186, 187] for detection of thymus hormone in urine Rehn found evidence of secondary hyperfunction of the thymus in some of these patients When iodine therapy relieved the thyrotoxicosis all evidence of thymus hyperfunction disappeared He believes that the myasthenia of exophthalmic goiter is the result of thymic hyperfunction

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PART III

ANTITHYROID GOITROGENS

Cyanates and Thiouracils

Compounds possessing antithyroidal properties fall into two general categories those that act without producing goiter such as iodine and radioactive iodine and those that cause marked hyperplasia of the thyroid and at the same time depress its function The latter group embraces the cyanides thiocyanates sulfonamides and thiourea with its derivatives This subject has been extensively reviewed by Williams[1] Riker and Wescoe Gargill and Lesses[3] and Greer[4]

The goitrogenic action of cabbage demonstrated in 19 9 by Chesney Clawson and Webster[4] was shown by Marine and his associates[5, 6] to be common to the entire genus of Brassica and to be due to contained cyanides The condition produced was in essence an iodine deficiency goiter, since it could be prevented by administered iodine and was due to increased thyroid activity caused by depressed oxygen consumption from the cyanide Depressed oxygen utilization increases thyroid activity goiter results if iodine is lacking in the face of added demands on the thyroid gland

That thiocyanates exert a goitrogenic and antithyroidal effect was first accidentally observed by Barker[7] in hypertensive patients under treatment with potassium thiocyanate Many similar cases subsequently reported have been reviewed by Estes and Keith[9] These goiters occur in about 4 per cent of such patients[8] and are characterized by thyroid hyperplasia the signs and symptoms of myxedema and occasionally by exophthalmos and by an increased *urinary excretion of inactivated* thyrotrophic hormone Rawson and his co workers[10, 11] believe that the thiocyanate prevents the synthesis of thyroid hormone at some point distal to the uptake of iodine since they were able to demonstrate excessive uptake of radio iodine by thiocyanate induced goiters Decreased hormone elaboration leads to hypometabolism with stimulation of the anterior pituitary and increased production of thyrotrophic hormone Thyroid hyperplasia results without a corresponding increase in hormone output — a hyperplasia of frustration The administration of desiccated thyroid prevents or relieves thiocyanate goiter

The more active substances were derivatives of thiouracil the less active possessed an aminobenzene group such as the sulfonamides and were a fourth as active as thiouracil The most potent of the former group proved to be 6 N propyl thiouracil in animal assays

To this periodic table of antithyroidal goitrogens established by Astwood other investigators [4–7] have added and undoubtedly will continue to add various active compounds since the slightest shift in chemical structure or linkage produces marked pharmacological differences

Since the morphological and physiological effects of these compounds particularly of thiouracil have been abundantly studied an accurate postulation of the mechanism of hormone inhibition can be constructed Thiouracil retards growth induces cretinism in newborn rats and antagonizes the effects of injection of the growth hormone of the anterior pituitary body [31, 3] The presence of the pituitary is essential for the production of goiter with these drugs [17, 8, 1] since no thyroid hyperplasia occurs in hypophysectomized animals following their administration in fact the thyroid gland regresses as in untreated hypophysectomized animals The goitrogenic effect results from pituitary stimulation and not from direct action by these compounds on the thyroid parenchyma (Plate 5)

No increase of thyrotrophic hormone is demonstrable in the blood or hypophysis of rats treated with thiourea or sulfadiazine in fact there is a decrease as compared with marked increases found in thyroidectomized animals [33] Animals pre treated with thiourea and then thyroidectomized showed an increase of thyrotrophic hormone in the blood and a decrease in the pituitary gland Gordon and his associates [33] state Thiourea and sulfadiazine by depressing the formation of active thyroid principle cause an increased release of thyrotrophin from the pituitary into the blood where however it appears in reduced amount because of its removal and increased utilization by the enlarging thyroid gland Although the decreased amount of the thyroid stimulating hormone found in the pituitary glands of the drug treated animals is not explained it has been shown by Albert and his associates [34, 3, 36] that physiologically inactive amounts of these goitrogens augment the action of the thyroid stimulating hormone when mixed with it in vitro and when administered in vivo This synergism is also illustrated by the greater hyperplasia of the thyroid gland in animals treated with both thiouracil and thyrotrophin as compared with that in animals treated with either alone

It has been noted above (Part II) that elementary iodine will inactivate thyrotrophin quite completely when the two are mixed in the test tube

Thiocyanate therapy may also cause acute goiter, clinically resembling thyroiditis [1] and pathologically showing extreme parenchymatous hypertrophy and hyperplasia [11] but without papillary infolding or lymphocytic infiltration. While the colloid stains well, the irregularity of the acini and a tendency toward invasiveness simulate neoplasia.

The antithyroidal and goitrogenic properties of the cyanides and cyanates were of experimental and toxicologic interest but failed of clinical application. In 1941, however, British and American investigators simultaneously revived interest in the chemotherapeusis of Graves' disease by parallel studies of new antithyroidal goitrogens. Kennedy and his co-workers [14] found that Brassica seed diets produced large goiters in rats in spite of simultaneously administered iodide; the goiters required the presence of thyrotrophic hormone for development or maintenance, since they did not develop in hypophysectomized animals and regressed after hypophysectomy [1] [16]. The active goitrogenic principle was demonstrated to be thiourea or allyl thiourea [17].

Meanwhile, Richter and Clisby [18], in searching for an improved rat poison, discovered that phenyl thiourea caused marked hyperplasia of the thyroid gland. Somewhat earlier, the MacKenzies and McCollum [19] found that sulfaguanidine caused marked thyroid hyperplasia.

In this initial phase of study, chief emphasis had been placed on goitrogenesis — an iteration of the early work with the cyanides and cyanates. Astwood and others [0] and simultaneously the MacKenzies [1] directed attention to the more important effect of these compounds as inhibitors of thyroid function. Both groups of investigators first studied the sulfonamides and thiourea, finding the latter many times more active as an antithyroidal drug. Both compounds caused thyroid hypofunction, with reduced oxygen consumption and impairment in growth and development. The thyroid glands were enlarged, hyperemic and hyperplastic with decreased colloid and increased acinar-cell height; papillary infoldings of the epithelium were frequently observed. Omission of the drugs was followed by histological and physiological return to normal. (Plates 3 and 4.)

The shifting of emphasis from goitrogenesis to antithyroidal activity was followed by widespread research into the compounds that maximally depressed thyroid function and were only incidentally productive of thyroid enlargement. Thiourea, thiouracil and their derivatives were found to be the most potent compounds for inhibiting thyroid function. In a study of over -20 substances Astwood, Bissell, and Hughes [3] found two types of chemical structure associated with antithyroidal activity:

Plate 3

4 Gross appearance of 3 thyroid glands dorsal aspect From left to right these are an untreated animal a 6-day old animal treated from the 21st day with 2 per cent sulfaguanidine in the diet and a 65 day-old rat treated from the [illegible] day with 5 per cent sulfaguanidine in the diet

5 Thyroid glands of female rats All sections were made in the same plane at right angles to the trachea and uniformly at a level near or through the parathyroids Hematoxylin and eosin

6 37 day-old animal which had received 5 per cent sulfaguanidine in the diet for 15 days

7 41 day-old rat hypophysectomized at 6 days of age and given 2 per cent sulfaguanidine in the food for 15 days This gland is indistinguishable from that of an untreated hypophysectomized rat

8 9 10 11 Glands taken at 2 4 and 12 days respectively after the beginning of treatment with 1 per cent thiourea in the drinking water at 21 days of age Treatment was discontinued at 7 days and figure 10 shows the degree of regression occurring in 5 days The epithelium is flat and colloid has reaccumulated but there is little decrease in size

From Astwood E B Sullivan J Bissell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endocrinology 1943 xxxii 2 0 25

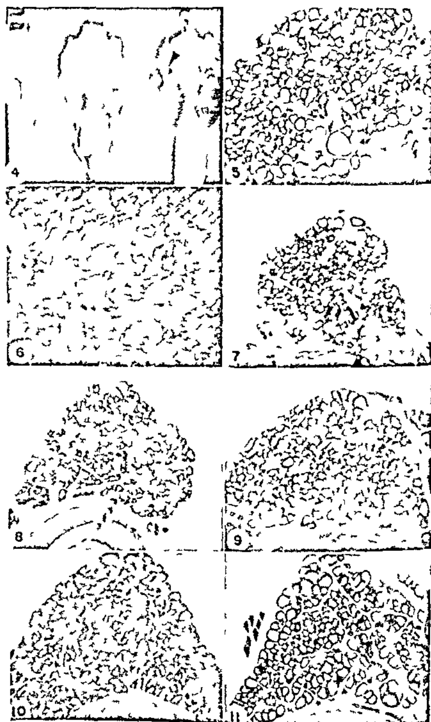

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Plate 4

12 Thyroid from a 33 day-old rat which had received a diet containing 2 per cent sulfaguanidine and 2 per cent thyroid powder for 13 days The gland is atrophic and resembles the gland in figure 7

13 Effect of 10 days treatment with 0 1 per cent thiourea and 1.0 per cent potassium iodide in the drinking water A minimal degree of inhibition of the thiourea is seen which is considered to be an effect of toxic amounts of potassium iodide

14 15 16 Glands from animals given 2 per cent sulfaguanidine in the food from the 21st to 51st days of life 14 Degree of hyperplasia induced by this treatment 15 Gland taken 5 days after hypophysectomy the drug being continued post-operatively 16 Thyroid of an unoperated animal 5 days after the drug was discontinued 15 and 16 show a reaccumulation of colloid and a flattening of the follicular epithelium

17 18 Glands of treated animals showing unusual types of hyperplasia 17 An adult treated with 1 per cent thiourea for 68 days 18 60 day-old animal which had received 0 5 per cent sulfapyridine in the drinking water for 11 days The follicular cells appear to be breaking away from their normal attachments and floating free in the colloid free follicular spaces

From Astwood L B Sullivan J Bissell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endocrinology 1943 xxxii 210-25


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Plate 4

12 Thyroid from a 33 day-old rat which had received a diet containing 2 per cent sulfaguanidine and 2 per cent thyroid powder for 13 days The gland is atrophic and resembles the gland in figure 7

13 Effect of 10 days treatment with 0.1 per cent thiourea and 1.0 per cent potassium iodide in the drinking water A minimal degree of inhibition of the thiourea is seen which is considered to be an effect of toxic amounts of potassium iodide

14 15 16 Glands from animals given 2 per cent sulfaguanidine in the feed from the 21st to 51st days of life 14 Degree of hyperplasia induced by this treatment 15 *Gland* taken 5 days after hypophysectomy the drug being continued post-operatively 16 Thyroid *of an unoperated animal 5 days* after the drug was *discontinued 15 and 16* show a reaccumulation of colloid and a flattening of the follicular epithelium

17 18 Glands of treated animals showing unusual types of hyperplasia 17 An adult, treated with 1 per cent thiourea *for* 68 days 18 60-day old animal which had received 0.5 per cent sulfapyridine in the drinking water for 11 days The follicular cells appear to be breaking away *from* their normal attachments and floating free in the colloid free follicular spaces

From Astwood L B Sullivan J Bissell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endocrinology 1943 xxxii 210-5



Plate 5

(upper) Thiouracil treated male and normal male litter mate control (age 10 weeks)
(lower) Same individuals as in upper (age 26 weeks) From Hughes A M Cretinism in rats induced by thiouracil Endocrinology 1944 xxxiv 69 76

Removal of most of the iodine results in reactivation of the hormonal material Albert and his co workers[34] have extended this original observation in a study of the in vitro effects of goitrogens and other reducing agents The goitrogens utilized were all thiourea derivatives including those that have been applied clinically An iodinated extract of thyrotrophin physiologically inactive was restored to potency by treatment in vitro with various thiourea derived goitrogens As these are reducing compounds various non goitrogenic reducing agents were studied and found to have similar but less marked effects in the reactivation of iodinated thyrotrophin

In addition to their ability to reactivate iodinated thyrotrophin these goitrogens were found capable of greatly augmenting thyrotrophic activity as measured by bio-assay[3] This augmenting effect was still present after removal of the goitrogen prior to bio assay so presumably there had been an alteration in the thyrotrophin itself which led to its increased activity

The capacity of thiourea derived goitrogens to augment thyrotrophin as well as to reactivate iodinated thyrotrophin was found to hold true in the living organism as well as in the test tube[36] In these experiments day old chicks were injected with iodinated thyrotrophin or active thyrotrophin after having previously received various amounts of thiouracil Marked augmentation of thyrotrophic potency up to 100 per cent and reactivation of iodinated thyrotrophin up to 50 per cent occurred in the thiouracil fed chicks

Whereas the goitrogenic action of the cyanides and probably of the cyanates could be inhibited by iodides this was not found to be true with the thiourea derivatives[37] which were in fact iodine resistant goitrogens But thyroxine or desiccated thyroid did prevent and abolish the goitrogenic and antithyroidal effect of these compounds as well as of the sulfonamides[1] indicating that they do not function by inhibiting the action of the thyroid hormone in the blood or peripheral tissues Moreover Malkiel[38] has found no destructive or inactivating effect of thiouracil and sulfaguanidine on endogenous circulating thyroxine

The effect of the antithyroidal goitrogens on the metabolism of iodine has been explored by conventional technics and through the use of radio active iodine Thiouracil and sulfadiazine cause nearly complete disappearance of iodine from the thyroid gland in five days[34] This effect is inhibited by removal of the hypophysis or administration of thyroxine Iodine reaccumulates after withdrawal of the drug but this reaccumulation is retarded by hypophysectomy or the administration of thyroxine



Plate 5

(upper) Thiouracil treated male and normal male litter mate control (age 10 weeks)

(lower) Same individuals as in upper (age 6 weeks) From Hughes A M Cretinism in rats induced by thiouracil Endocrinology 1944 xxxiv 69 76

collected radio-iodine in larger quantities than did those of the controls, in amounts similar to those collected by glands made hyperplastic with injections of thyroid stimulating hormone The inhibition of iodine collection resulting from thiouracil in the intact thyroid gland contrasts sharply with the in vitro studies previously described [4, 43] but both sets of experiments confirm the hypothesis that thiouracil interferes with hormone synthesis by interfering with the metabolism of iodine Thiouracil inhibited collection of radio-iodine by normal chick thyroid and by that made hyperplastic through thyroid stimulating hormone or thiouracil Salter Cortell and McKay [47] reached similar conclusions concerning the role of thiouracil—it prevents the conversion of iodide to diiodotyrosine and thyroxine without however impeding the synthesis of uniodinated thyroid protein

Chaikoff and his associates [48] have confirmed the depressing effect of potassium thiocyanate on the uptake of radio-iodine by thyroid tissue either in vitro or in living animals maintained on an iodine poor diet Following the disappearance of potassium thiocyanate from the circulation the whole gland does have an increased uptake of radio iodine but this increase is not apparent when expressed in terms of unit weight of tissue Thus the drug interferes with the removal of iodine from the circulation when iodine is not readily available in the diet It also inhibits conversion of inorganic iodide to diiodotyrosine and thyroxine as shown by low thyroxine content of the gland and decreased levels of protein bound iodine in the blood Vanderlaan and Bissell [49] have confirmed this course of events by showing that rats fed propylthiouracil readily take up radio iodine in their thyroid glands but retain it only for a short time possibly because it is not hormone bound and that in the presence of both propylthiouracil and potassium thiocyanate there is delayed and only moderate iodine uptake by the gland They conclude that in the presence of thiocyanate the ability of the thyroid gland depleted of iodine to take up injected iodine is considerably impaired

Vanderlaan and Vanderlaan while studying the iodine concentrating mechanism of the rat s thyroid found that thiocyanate interfered significantly with this mechanism by preventing the uptake of iodide as such and also by causing discharge of iodide stored in the thyroid Astwood had previously shown that the thyroid could concentrate iodine independently of its ability to manufacture hormone The iodine initially absorbed by the gland was shown by the Vanderlaans to be present as iodide that was ultra filtrable and behaved as iodide potentiometrically These investigators have introduced the concept of a gradient between

The relation between the dose of thiouracil and thyroid weight and iodine content is quantitative enough to be used for the assay of new compounds [39, 40]

By in vitro studies of thyroid slices with radioactive iodine Franklin and Chaikoff [41] found that the sulfonamides inhibited the formation of diiodotyrosine and thyroxine but did not alter the absorption of inorganic iodide from the surrounding medium Thiouracil and thiocyanate were similarly shown by these investigators [4] to depress or inhibit the formation of thyroxine and diiodotyrosine in vitro They differed in their effect on iodine concentration by thyroid slices, thiouracil having little effect and thiocyanate causing marked depression of iodine uptake by the surviving tissues

The inability of large amounts of iodine to overcome the stasis of hormone production caused by thiourea was demonstrated in rabbits by Baumann Metzger and Marine [37] who showed that the drug caused rapid decrease in both thyroxine and non thyroxine iodine in the gland itself with excretion of the excess iodine in the urine Further studies in vivo with radio iodine have confirmed the result of the studies in vitro—namely that thiouracil interferes in the living animal with the incorporation of iodine into thyroxine and diiodotyrosine in the thyroid gland [43] and thus causes cessation of hormone synthesis

Further details of the mechanism of action of thiouracil on iodine metabolism have been supplied by studies on the chick with radio iodine It was first demonstrated that thyrotrophic hormone produces thyroid hypertrophy within 24 hours [44] but no increased iodine uptake occurred until hyperplasia was marked This accelerated uptake was not maintained with continued stimulation In addition thyrotrophic hormone caused early and striking acceleration in the loss of radio iodine from the gland so that 75 per cent of the quantity initially stored was lost during the first day This was interpreted as being due to accelerated secretion of thyroid hormone from the gland induced by thyrotrophic stimulation

Next a comparison was made of the effects of thiouracil and of thyrotrophic hormone on the collection of radio iodine and on the histology of the thyroid gland in the chick [4, 46] The histological changes produced were indistinguishable except for a lag of five days in the appearance of alterations caused by thiouracil Within an hour after the injection of thiouracil however maximal inhibition of the uptake of radio iodine occurred with a gradual loss of this inhibitory effect over 24 hours Following the withdrawal of thiouracil the glands of the treated chicks

collected radio iodine in larger quantities than did those of the controls in amounts similar to those collected by glands made hyperplastic with *injections of thyroid stimulating hormone* The inhibition of iodine collection resulting from thiouracil in the intact thyroid gland contrasts *sharply with the in vitro studies previously described* [4, 43] but both sets of experiments confirm the hypothesis that thiouracil interferes with hormone synthesis by interfering with the metabolism of iodine Thiouracil inhibited collection of radio iodine by normal chick thyroid and by that made hyperplastic through thyroid stimulating hormone or thiouracil. Salter Cortell and McKay [47] reached similar conclusions concerning the role of thiouracil—it prevents the conversion of iodide to diiodotyrosine and thyroxine without however impeding the synthesis of uniodinated thyroid protein

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the concentration of iodide in the serum and in thyroid tissue Over a considerable range of serum iodide concentration they found this gradient to be constant Thus the concentration of iodide in the thyroid could be viewed as a function of the level of the serum iodide In normal glands the concentration of iodide was 25 times that of the serum whereas in animals pretreated with propylthiouracil there existed a tenfold increase in this concentrating power

A new technique for the assay of antithyroid compounds in normal human subjects has been described by Stanley and Astwood The uptake of tracer doses of radio iodine was first determined in clinically normal persons and then the inhibitory action of a single dose of various thiourea and thiouracil compounds upon this uptake was measured by a Geiger Muller counting tube which was placed directly over the thyroid gland Serial counts were taken at frequent intervals With this method 32 compounds were assayed in 90 subjects and it was found that the values realized differed considerably from those found by rat or chick assay and indeed agreed much more closely with clinical appraisals of relative potency It is of interest that sulfadiazine, the only member of the aminobenzene group of antithyroid compounds tested, was found to be inert by this method contrasting very sharply with its considerable effectiveness in animals

The evidence that biosynthesis of thyroxine is intracellular aerobic and enzymatic has been discussed in Part 1 The iodination of tyrosine to diiodotyrosine requires liberation of iodine from iodide The formation of diiodotyrosine and thyroxine is linked with aerobic oxidations involving the cytochrome-cytochrome oxidase system [3] The effect of the sulfonamides and thiouracil on this enzyme system is controversial Franklin and Chaikoff [41] observing no effect with the sulfonamides and Dempsey [4] noting that thiouracil readily inhibited the peroxidase reaction in thyroid tissue but did not affect the cytochrome oxidase reaction McShan Meyer and Johansson found no inhibition of cytochrome oxidase or of succinoxidase in thyroid tissue by sulfonamides and thiouracil On the other hand Paschkis and his co-workers [6] report that thiouracil and the sulfonamides inhibit the cytochrome-oxidase in vitro as well as in the thyroid gland itself Bevelander [7] after studies on sea urchin egg development concluded that thiourea acts by inhibition of enzyme systems necessary for the growth of the sea urchin Tipton and Nixon [58] observed significant depression of succinoxidase and cytochrome oxidase in the liver of rats

Thiouracil acts by preventing iodination and hormone synthesis but it is still not clear whether it acts as an anti oxidant through depression

of the enzyme systems or by some mechanism other than inhibition of oxidation

The differentiation of the antithyroidal and goitrogenic actions of thiourea derivatives sulfonamides and para aminobenzoic acid (PABA) by the response of the organism to iodine administration has been established by Mackenzie [8] Small amounts of iodide markedly inhibited the thyroid enlargement as measured by weight caused by thiouracil but had no significant effect on the thyroid hyperplasia Large amounts of iodide had no further effect on thyroid weight but did suppress the hyperplasia With very large amounts of iodide the morphological response to thiouracil was repressed and in fact resembled the glands found in thyrotoxicosis following the administration of iodides i e reduced hyperemia decreased cell height colloid filled follicles but no complete suppression of epithelial hypertrophy

The administration of iodide to sulfaguanidine treated rats did not reduce thyroid weight or inhibit the degree of hyperplasia There was instead a potentiation of the goitrogenesis effected by the sulfaguanidine with increased weight and some tendency toward decreased colloid content Mackenzie notes This is probably the only condition thus far described in which iodide does not have an inhibiting effect on thyroid hyperplasia

Iodide administration in rats fed PABA had an effect similar to that found in the rats to whom the thioureas were administered — namely inhibition of goitrogenesis and hyperplasia The mechanisms may be different but the end results are the same so far as the thyroid gland is concerned

Further insight into the action of the goitrogens may eventually be gained through recent knowledge of their antibacterial and antitoxic effects Thus Weinstein[illegible] and Strandskov and Wyss [81] have found that thiourea is bacteriostatic for gram negative organisms inhibiting their growth and metabolism Zahl and his co workers[illegible] have demonstrated that both thiouracil and PABA have a protective effect against salmonella endotoxin apparently through interference with thyroid activity

Thiourea not only depresses enzymatic and bacterial metabolism but also disturbs the biochemical balance of the organism sufficiently to produce tumor formation Thus Purves and Griesbach[illegible] found that the prolonged administration of thiourea to rats resulted in the formation of thyroid adenomas many of which ultimately developed the histological characteristics of adenocarcinoma with blood vessel invasion and pulmonary metastases (Plates 6 7 8 9)

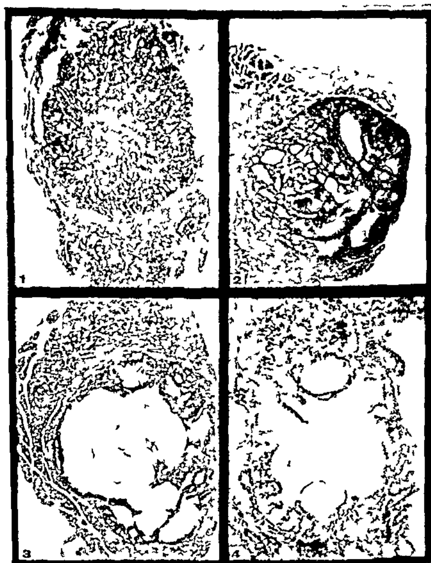

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Plate 6

1 Thyroid of rat after 17 month of rape seed diet One large several smaller adenomata Little normal thyroid tissue remaining Azan Stain

2 17 months rape seed diet Adenoma forming nodule projecting from the thyroid surface Compressed thyroid tissue forming a pseudocapsule H & E Stain

3 17 months rape seed diet Large adenoma showing cystic spaces filled with dilute colloid The darker staining of the adenoma tissue is apparent Azan Stain

4 Part of same tumor as 3 showing mechanism of formation of cystic spaces by rupture of acinar walls H & E Stain

From Griesbach W E Kennedy T H and Purves H D Studies on experimental goiter VI Thyroid adenomata in rats on Brassica seed diet Brit Jour Exper Path., 1945 xxvi 18 24

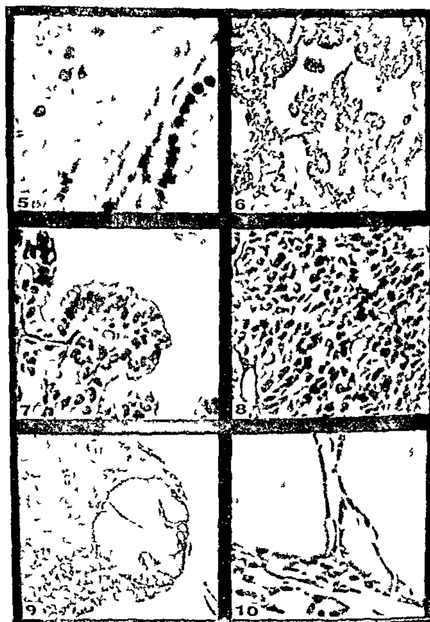

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Plate 7

5 Top left normal hyperplastic thyroid tissue Lower right edge of adenoma, showing the columnar form and darker staining nuclei of the adenoma cells H & E Stain

6 Adenoma of 1 showing papillary type of epithelial growth Azan Stain

7 Part of 6 Azan Stain

8 From an adenoma showing undifferentiated type of growth H & E Stain

9 17 months rape seed diet thyroxine injected during last three weeks The cystic adenoma is filled with dense colloid and the epithelium is flattened H & E Stain

10 Part of 9 showing flattened epithelium after thyroxine treatment H & E Stain

From Griesbach W E Kennedy T H and Purves H D Studies on experimental goiter VI Thyroid adenomata in rats on Brassica seed diet Brit Jour Exper Path., 1945 xxvi 18 4

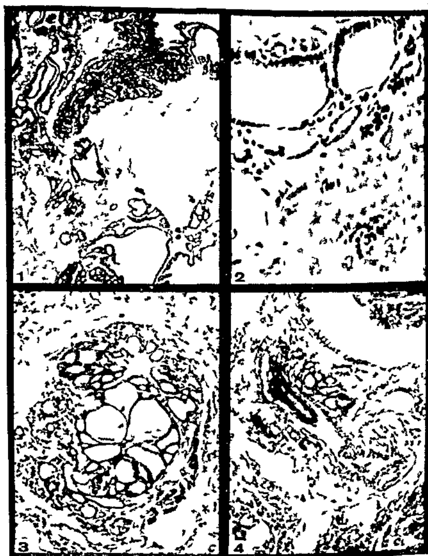


Plate 8

1 Thyroid gland of Rat No 1 showing adenocarcinoma Colloid accumulation and areas of papillary growth are shown The wall of the vein to the right of the figure is extensively invaded by the tumor H & E Stain

2 Another field of the section shown in 1 showing tumor cells in contact with the blood stream H & E Stain

3 *Metastasis in lung of Rat No 1 The central area containing large acini is surrounded by an area characterized by imperfect acini formation* H & E Stain

4 Lung of Rat No A metastasis is situated inside a branch of the pulmonary artery An extension of this growth is infiltrating the tissues outside the artery H & E Stain

From Purves H D and Griesbach W E Studies on experimental goiter VII Thyroid carcinomata in rats treated with thiourea Brit Jour Exper Path 1946 xxvii 294 7

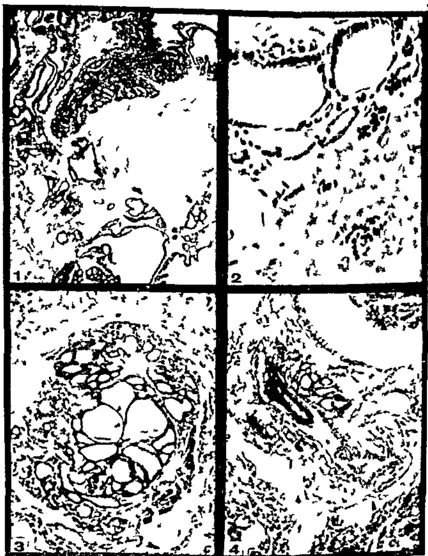

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Plate 9

5 Thyroid gland of Rat No 2 showing at the top of the figure some normal thyroid tissue Below this is adenocarcinoma and at lower right the edge of a nodule of fetal adenoma H & E Stain

6 Thyroid gland of Rat No 2 showing thyroid carcinoma on the left In the center is a vein containing carcinoma tissue in the lumen H & E Stain

7 Lung of Rat No 2 showing a branch of the pulmonary artery in cross section The artery contains a small thyroid metastasis consisting of two acini containing colloid The metastasis is covered with endothelium and the remainder of the lumen is patent and contains blood H & E Stain

8 Lung of Rat No 2 showing a thyroid metastasis consisting of a single acinus distended with colloid H & E Stain

From Purves H D and Griesbach W E *Studies on experimental goiter VII Thyroid carcinomata in rats treated with thiourea* Brit Jour Exper Path 1946 xxvii 294 7


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tration in the body or in the thyroid gland in relation to antithyroidal activity but no parallelism could be established. Storage of these goitrogens in the thyroid gland was clearly not the factor that determined their thyroid inhibiting effect.

Other Antithyroidal Agents

The effectiveness of the antithyroidal goitrogens depends on their interference with the production of thyroid hormone. They do not in themselves antagonize or neutralize the effect of circulating thyroxine so that they are antithyroidal by indirection rather than specifically. Recently certain compounds have been claimed to be particularly antagonistic to thyroxine itself. Carter and his collaborators [illegible] found a substance in ox and whale liver and in human urine—identified as paraxanthine (1, 7-dimethylxanthine)—that was capable of converting the temperature heart rate curve of the summer frog's heart into the curve of the winter frog's heart. This substance, which was isolated in crystalline form, appeared to counteract the effects of thyroxine in rats. Barker and Williams [78] however, were unable to find significant antithyroidal action from this drug as measured by effects either on oxygen consumption or on tadpole metamorphosis. It had no observable result when given to a thyrotoxic patient for a period of 11 days.

Mansfeld extracted from the thyroid gland and human serums crystalline substances called thermo thyrin A and B that are capable of producing as much as a 30 per cent lowering of oxygen consumption in rats. This work has not yet been confirmed but the compounds involved may be related to certain structural analogues antagonistic to thyroxine investigated by Wooley [80]. These newly synthesized ethers of N-acetyl diiodotyrosine counteracted the pharmacological effects of thyroxine on tadpoles. The presence of an iodine atom or atoms in a benzenoid nucleus of a compound itself devoid of thyromimetic action is a necessary characteristic for this inhibitory effect. Niemann [81] has commented that the relationship of the structure of the inhibitor to that of thyroxine may indeed be of a remote nature.

Lawson and Rimington [illegible] in searching for a natural antithyroidal thiol compound studied ergothioneine, a normal constituent of the blood. Ergothioneine is methyl betain of 2-thiol-histidine. When administered to rats it was found to exert an antithyroidal effect comparable to that of thiouracil. Clinical studies have not yet been reported.

The anatomical effects produced in the human thyroid gland by thiouracil have been studied chiefly in the hyperplastic gland of Graves' disease. The size of the gland may increase, decrease, or remain unaltered, but the gross increases in human beings have not been so striking or so constant as those in experimental animals. Prolonged treatment has usually resulted in a decrease of the gland[64] unless myxedema supervenes. Histologically, however, there is great similarity to the experimental effect, with increased thyroid hyperplasia, loss of colloid and increased vascularity.[6, 68] Changes in the pituitary gland similar to those found in animals—increased basophilism and absent eosinophilism—have been reported.[6]

Physiologically, thiouracil decreases the basal metabolic rate, frequently at the same rate as iodine,[6, 68] and in many cases causes clinical myxedema if continued for several months.[68, 69] Myxedema however has not yet been readily produced by thiouracil in persons with normal thyroid function,[68] the normal economy evidently possessing adequate homeostatic mechanisms for resisting the usual goitrogenic and thyroid depressing effects of this compound. Following the administration of thiouracil in Graves' disease the uptake of tracer doses of radioiodine is greatly diminished, with an increased urinary excretion,[6] as previously described in animal studies. The hormonal iodine of the blood returns to normal,[70] the blood cholesterol rises,[71] the calcium, phosphorus and protein balances become more positive, and creatinuria decreases.[7] In general the physiological effects produced are such as would occur with amelioration of thyrotoxicosis and a return to the euthyroid state. These changes, which occur far more regularly than with iodine therapy, may take from several weeks to several months for completion.

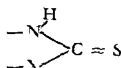
The absorption, distribution and metabolism of thioureas and thiouracils have been studied by Williams and his co-workers[3, 74] through application of methods of considerable accuracy to all the tissues and fluids of the body. Thiouracil is rapidly absorbed from the gastro-intestinal tract and appears in the blood stream within 15 minutes after ingestion. It is present chiefly in the cells of the blood, bound to protein, and rarely in concentrations above 6 mg per cent. It diffuses into all the tissues and fluids, where about half of it is degraded. A small amount is destroyed in the gastro-intestinal tract, and about one third is excreted unchanged in the urine. It passes through the placenta in biologically active quantities. It is excreted in milk and can produce cretinism in suckling animals.[7]

Various thiouracils have been studied further[4] with regard to concen

A new antithyroidal goitrogen differing chemically from previously known substances has been discovered by Bull and Fraser.[83] They observed three patients who had developed myxedema and goiter following the prolonged application of resorcinol ointment to varicose ulcers of the legs. Biopsies of the thyroid gland in these patients showed intense hyperplasia similar to that found after the thiouracils. The level of the protein-bound iodine in the blood was extremely low but the uptake of radioactive iodine was high as soon as the resorcinol applications were omitted. In this manner the action of resorcinol was like that of the thiocyanates and the thiouracils, depressing iodine binding by the thyroid gland with resultant hyperplasia and permitting great iodine avidity upon omission of the goitrogen. Further studies by Doniach and Fraser[84] of the effects of resorcinol upon the thyroid gland of the rat indicated that, like the thiouracil compounds, this drug markedly depressed iodine uptake and organic binding of iodine.

A goitrogen with marked stimulatory adrenal as well as antithyroidal effects is Amphenone B, a substituted desoxybenzoin. Hogness and his associates[85] have shown that this compound inhibits the incorporation of I^{131} into thyroid protein both in vivo and in vitro with a potency equal to that of propylthiouracil and without any effect on the rate of release of radio-iodine from the rat thyroid. Prolonged administration to rats produced adrenomegaly which was associated with increases in adrenal ascorbic acid and cholesterol concentrations. Determinations of liver glycogen, circulating eosinophiles and thymus weight indicated that the enlarged adrenals were capable of responding to ACTH or cold stimulus by secreting an increased quantity of steroids. The response in Amphenone-'B'-treated animals was greater than that of the controls.

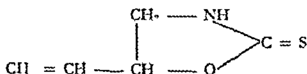
Greer,[86] in a review of the relation of plant and animal products to goitrogenesis, points out that the thionamide grouping is characteristic of the antithyroidal goitrogens active in man and that vinyl thiooxazolidone is the only antithyroid compound that has been isolated from ruta-





Thionamide Grouping

baga and other members of the cabbage family. This compound exists in nature in combined form, possibly as a glycoside. If the roots or seeds



L-5-vinyl-2-thiooxazolidone

are boiled, baked, or steamed, no thiooxazolidone can be isolated, but if the raw food is finely ground and suspended in water, the thiooxazolidone is formed in a few minutes. The heated, inactivated material will, however, yield thiooxazolidone if it is subsequently treated with a purified enzyme preparation from the unheated plant. The compound has never been isolated from cabbage leaves, and this probably accounts for the fact that cabbage as ingested by man seems to have very little antithyroid activity. Greer concludes that while a sporadic goiter in man may occasionally be due to the ingestion of goitrogenic foods, very few instances of thyroid enlargement not due to iodine lack have yet been explained. It is possible, of course, that other naturally occurring goitrogens may be isolated in the future from other foods and that these may not require enzymatic liberation to acquire antithyroidal activity.

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PART IV

THE METABOLISM OF IODINE AND ITS RELATION TO THE STRUCTURE AND FUNCTION OF THE THYROID

Absorption and Excretion of Iodine

The absorption and excretion of iodine involves the following factors (1) the level of iodine intake (2) the type of iodine compound administered (3) the state of thyroid function and (4) the route of administration Elmer[1] and Salter have reviewed this subject from the standpoint of iodine balance Techniques utilizing radioactive isotopes have added further information on the absorption storage and excretion of iodine

In normal persons maintained on a low intake of iodine Puppel and Curtis[3] found that about 70 per cent of the iodine was excreted in the urine 15 per cent in the feces and the remaining 15 per cent in the perspiration Negative iodine balance readily ensued with a sufficiently low intake of iodine

With quantities of iodine ranging from 20 to 440 mg daily amounts markedly in excess of any physiological requirements Nelson and his associates[4] found that iodine was rapidly absorbed with plasma iodine concentrations running parallel to the level of intake The absorption was both rapid and complete since no significant quantity of iodine was recovered from the feces Iodine disappeared from the plasma at a relatively uniform rate in accordance with the level of concentration so that after 24 hours the plasma iodine concentration had returned almost to normal About 75 per cent of the iodine was excreted in the urine within the first 3 days after a large intake Between 2 and 10 per cent of the iodine was excreted in the perspiration as had been previously demonstrated by von Fellenberg[5] In profuse sweating the latter had observed excretion values of over 30 per cent The fecal excretion was found negligible by Nelson[4] but Cole and Curtis[6] reported that 6 to 7 per cent of the iodine intake was excreted in the feces

In non toxic nodular goiter Puppel and Curtis[7] noted excretion values

balance in these individuals but excessive amounts of ingested iodine did effect a positive iodine balance (Figs 16 17 18 19 20)

Iodine in organic combination such as in di iodotyrosine and thyroxine is readily absorbed from the gut with minimal fecal loss Thyroxine itself is easily absorbable if administered in alkaline solution but is largely excreted in the feces when administered in its dry crystalline and quite insoluble state Thyroid substance is readily assimilated and in myx

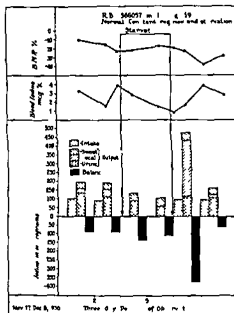


Fig 17 The effect of starvation on the normal iodine balance Note the continued negative balance

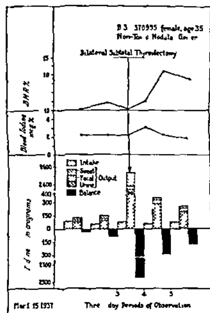


Fig 18 Non toxic nodular goiter presents a normal negative iodine balance on a low iodine intake Note the effect of thyroidectomy

From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574-87

edema produces a greater effect than its contained thyroxine (see Part 1)

The significance of the form in which iodine is administered has recently been emphasized by Dvoskin[8] who has successfully demonstrated the thyroxine like action of elemental iodine in the experimental animal Many previous investigators had demonstrated that elemental iodine administered parenterally would induce metamorphoses in the axolotl even after thyroidectomy or hypophysectomy This effect could not

of iodine entirely comparable to those in normal human beings at corresponding levels of intake, whereas in thyrotoxicosis the same author[3]

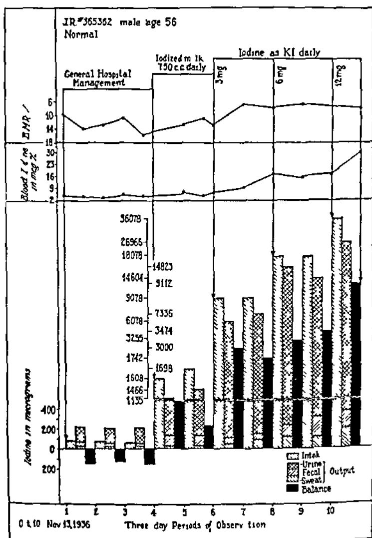


Fig 16 The iodine balance in a normal individual Note the negative iodine balance on a low iodine intake and the effect of increasing the intake From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574 87

demonstrated a great increase in iodine excretion especially in the feces A normal iodine intake in thyrotoxic patients resulted in negative iodine

to prevent thyroid hypertrophy and increase in gland weight by the administration of the goitrogens thiouracil and sulfadiazine

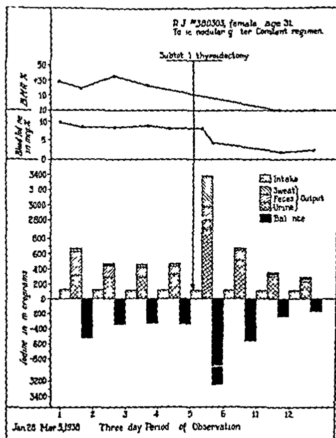


Fig 20 The increased negative iodine balance of toxic nodular goiter Note the increased urinary excretion over normal Note the effect of thyroidectomy From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 5 4 87

By these criteria elemental iodine when administered subcutaneously was found to have a thyroxine like action that was not evident on oral administration

Iodine Stores in the Body

While iodine storage in the organism occurs mainly in the thyroid gland significant concentrations of this element occur throughout the

be produced by addition of elemental iodine to the water in which the axolotl was kept The subcutaneous injection of elemental iodine in the rat or chick produced effects similar to those produced by thyroxine whereas sodium iodide when injected had little thyroxine like activity The methods utilized in these studies as a measure of thyroxine like activ

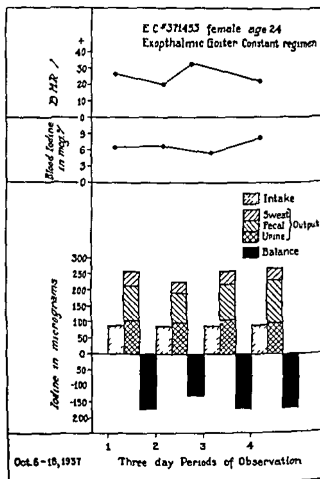


Fig 19 The increased negative iodine balance of exophthalmic goiter Note the increased fecal excretion over normal From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574 87

ity were (1) the ability to restore and maintain growth after thyroidectomy, (2) the ability to restore the adrenal gland weight of thyroidectomized rat to normal (3) the ability to cause involution of thyroid epithelium and to decrease gland weight in normal rats, and (4) the ability

to prevent thyroid hypertrophy and increase in gland weight by the administration of the goitrogens thiouracil and sulfadiazine

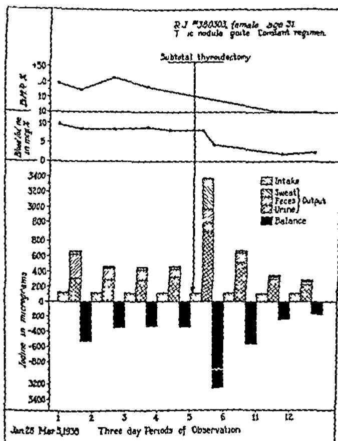


Fig o The increased negative iodine balance of toxic nodular goiter Note the increased urinary excretion over normal Note the effect of thyroidectomy From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574 87

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Iodine Stores in the Body

While iodine storage in the organism occurs mainly in the thyroid gland significant concentrations of this element occur throughout the

body chiefly in the form of iodides Salter[9] has elaborated available knowledge of intrathyroidal and extrathyroidal iodine storage into a concept of iodide circulation This circulation permits release of hormonal iodide for its metabolic function and also allows the utilization of released iodide for re-synthesis of thyroid hormone Iodine in the tissues is present as inorganic iodide or as organic iodine in the form of thyroxine or diiodotyrosine or perhaps as triiodothyronine The distinction between iodine as iodide and iodine as hormone has lost some of its importance in the light of the previously mentioned research of Dvoskin[8]

The iodine stores in the body tissues have assumed new importance since the use of radioactive iodine in therapy and investigation for tissue absorption of radio iodine may lead to effects on other organs than the thyroid The total iodine content of the body generally is between 20 and 50 mg of which about 20 per cent resides in the thyroid gland In this gland iodine is many hundreds of times more concentrated than in other tissues except for other endocrine glands especially the gonads hypophysis adrenals, and parathyroids The mass of skeletal muscles is so large that its total iodine content is high in fact containing the major portion of the body iodine but the iodine concentration per gram of tissue is 1/1000 that of the thyroid The increased concentration of iodine in the endocrine glands will disappear after thyroidectomy whereas muscle and tissue iodine decrease only slightly This minor decrease in muscle iodine after thyroidectomy has been shown by Salter[10] to be due to loss of organically bound iodine from the muscles that contain both inorganic iodide and organic iodine

The thyroid itself under normal conditions has approximately 50 000 gamma per cent (50 mg per cent) of iodine

The iodine concentration in endocrine glands other than the thyroid is not large but may be of physiological importance The anterior pituitary contains from 80 to 190 gamma per cent[1, 13] whereas the posterior lobe contains considerably lower amounts

The iodine content of the adrenal cortex has been reported by Elmer and Scheps[14] as varying between 6 and 66 gamma per cent of dried tissue whereas the medullary content was found to be about 16 to 0 gamma per cent The ovaries contain relatively large amounts of iodine Maurer[15] Sturm and Bucholz[1] Carter[16] and Perkin and Brown[17] have all found concentrations of iodine in the ovary second only to those found in the thyroid itself The actual amounts found in various animals as well as in humans has been estimated to vary from 30 to 741 gamma per cent The testes have been found relatively low in iodine content[1]

Iodine Requirements and Iodine Balance

The iodine requirement of the organism has been studied by balance studies utilizing the usual techniques of measuring intake and output and by the indirect method of determining the minimal intake of iodine that will prevent goitrogenesis Both methods are subject to considerable experimental error balance studies deal with such minute amounts of iodine that technical errors readily occur, while histological changes may be late in appearance

The minimal daily requirement of iodine as estimated by balance studies lies between 15 and 25 micrograms according to Cole and Curtis[6] However Puppel and Curtis[7] as well as Scheffer[19] have found negative balances in some normal individuals receiving from 30 to 110 micrograms daily and Puppel and Curtis consider 50 to 100 micrograms as the minimal iodine need If one calculates the amount of iodine utilized daily in the form of thyroxine for the maintenance of normal thyroid function in myxedematous patients values ranging from 163 to 3 5 micrograms of iodine are realized[14, 3] The excess iodine over that found in balance studies is probably re synthesized into thyroid hormone Growth and increased total metabolism from whatever source augment the need for iodine Infants for instance have a larger iodine need when this is referred to either body weight or surface area

The Marine Cycle The Effect of Iodine Deficiency upon Thyroid Structure

Before modern microchemical techniques had become available for accurate balance studies Marine and his co workers[1, 2, 3, 4, 5, 6] had demonstrated most of the significant facts concerning the relation of the level of iodine intake to thyroid structure Marine found the following (1) iodine is necessary for normal thyroid function and morphology (2) iodine is rapidly taken up by the thyroid gland (3) the amount of iodine available determines the degree of hyperplasia in an inverse ratio (4) all hyperplasia of the thyroid is anatomically and chemical identical (5) thyrotoxicosis is regularly associated with thyroid hyperplasia with an inverse relation of iodine content to the degree of hyperplasia, (6) hyperplasia involutes to a colloid goiter or rarely results in exhaustion atrophy depending upon opportunities for a physiological rest as provided by iodine (see Table 1 and Fig 1)

body chiefly in the form of iodides Salter[9] has elaborated available knowledge of intrathyroidal and extrathyroidal iodine storage into a concept of iodide circulation This circulation permits release of hormonal iodide for its metabolic function and also allows the utilization of released iodide for re synthesis of thyroid hormone Iodine in the tissues is present as inorganic iodide or as organic iodine in the form of thyroxine or diiodotyrosine or perhaps as triiodothyronine The distinction between iodine as iodide and iodine as hormone has lost some of its importance in the light of the previously mentioned research of Dvoskin[8]

The iodine stores in the body tissues have assumed new importance since the use of radioactive iodine in therapy and investigation for tissue absorption of radio-iodine may lead to effects on other organs than the thyroid The total iodine content of the body generally is between [illegible]0 and 50 mg, of which about [illegible]0 per cent resides in the thyroid gland In this gland iodine is many hundreds of times more concentrated than in other tissues except for other endocrine glands especially the gonads hypophysis adrenals and parathyroids The mass of skeletal muscles is so large that its total iodine content is high in fact containing the major portion of the body iodine but the iodine concentration per gram of tissue is 1/1000 that of the thyroid The increased concentration of iodine in the endocrine glands will disappear after thyroidectomy whereas muscle and tissue iodine decrease only slightly This minor decrease in muscle iodine after thyroidectomy has been shown by Salter[10] to be due to loss of organically bound iodine from the muscles that contain both inorganic iodide and organic iodine

The thyroid itself under normal conditions has approximately 50 000 gamma per cent (50 mg per cent) of iodine

The iodine concentration in endocrine glands other than the thyroid is not large but may be of physiological importance The anterior pituitary contains from 80 to 190 gamma per cent[12, 13] whereas the posterior lobe contains considerably lower amounts

The iodine content of the adrenal cortex has been reported by Elmer and Scheps[14] as varying between 26 and 66 gamma per cent of dried tissue whereas the medullary content was found to be about 16 to [illegible]0 gamma per cent The ovaries contain relatively large amounts of iodine Maurer[15] Sturm and Bucholz[16] Carter[16] and Perkin and Brown[17] have all found concentrations of iodine in the ovary second only to those found in the thyroid itself The actual amounts found in various animals as well as in humans has been estimated to vary from 30 to 741 gamma per cent The testes have been found relatively low in iodine content[1]

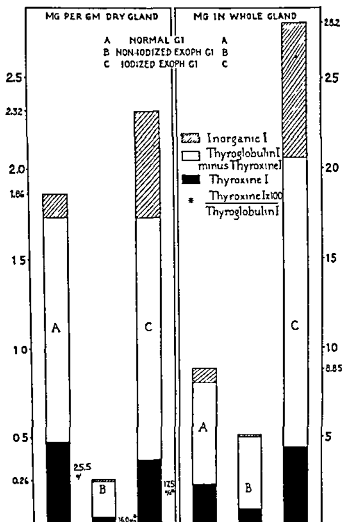


Fig 21 The average total iodine thyroxine iodine and inorganic iodine of 70 normal 44 non iodized and ,0 iodized exophthalmic glands are compared in terms of mg per gm of dry gland and mg in the hole gland A is based on data of Leland and Foster and our own B is calculated from Wilson and Kendall From Gutman A B Benedict E M Baxter B and Palmer W W The effect of administration of iodine on the t tal iodine inorganic iodine and thyroxine content of the pathological thyroid gland Jour Biol Chem 1932 xcvii 303 24

TABLE I

THE RELATION OF IODINE TO THYROID STRUCTURE (THE MARINE CYCLE)
BASED ON DATA OF MARINE AND WILLIAMS

	Normal	*Early Hyperplasia*	*Moderate Hyperplasia*	*Marked Hyperplasia*	*Colloid Goiter*
Wt Fresh Gland gm /kg Body Wt	0 36 →	0 30 →	0 9 →	2 34	1.07
Conc of Iodine mg /gm fresh thyroid	0 78 →	0 14 →	0.08 →	0 0	0.46
Total Iodine in gland mg	1.42 →	0.44 →	0 54 →	0 29	3 23
					Exhaustion Atrophy

The only histological cycle which the thyroid follicle and its component cells are capable of undergoing is that described by Marine [7] and consists essentially in a progression from normal through varying degrees of hyperplasia to colloid goiter or exhaustion atrophy The colloid goiter represents a resting phase and is the closest approach to normal which a gland once hyperplastic can exhibit The colloid gland in turn may itself under appropriate conditions become hyperplastic and again become colloid or develop exhaustion atrophy In the latter condition, seen most frequently in endemic cretinism and in the late stages of hyperthyroidism there is loss of uniformity of the cells of the follicle wall with disintegration and desquamation of cells great irregularity and pyknosis of the nuclei with marked reduction of colloid Cell death reduces the size of the follicle with relative or absolute increase in the surrounding stroma

According to Marine s studies therefore the stimulus to hyperplasia arises whenever the amount of thyroid tissue is inadequate to supply sufficient hormone either as a result of reduced iodine intake by increased demands for thyroid hormone, or from partial thyroidectomy These changes are mediated through thyrotrophic stimulation

BLOOD IODINE

The level of total blood iodine measures both the iodine transported from the gastro intestinal tract to the thyroid gland and the hormonal iodine circulating from the gland to the tissues Kendall and Richardson [8] showed that normal blood contained iodine in a characteristic range This range has been found to lie between 5 and 20 gamma or

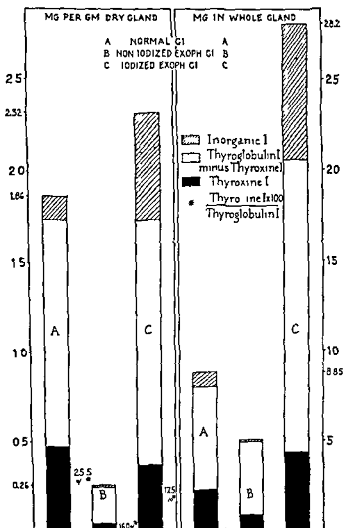


Fig 21 The average total iodine thyroxine iodine and inorganic iodine of 70 normal 44 non iodized and 70 iodized exophthalmic glands are compared in terms of mg per gm of dry gland and mg in the whole gland A is based on data of Leland and Foster and our own B is calculated from Wilson and Kendall From Gutman A B Benedict L M, Baxter B and Palmer W W The effect of administration of iodine on the total iodine inorganic iodine and thyroxine content of the pathological thyroid gland Jour Biol Chem 1932 xcvii 303 4

micrograms per hundred cc of blood (1 gamma or microgram = 0.001 mg or 1/1000 mg) Temporary increases in these values to non physiological ranges will occur following the ingestion of iodides—for example Nelson and his associates[4] found concentrations up to 1500 micrograms when iodides were ingested by normal human subjects The relationship between plasma iodine concentration and iodine intake was linear The rate of disappearance of iodine from the plasma was also linear, so that basal values were attained within 72 hours

Early studies of blood iodine were largely confined to total iodine determination and required as much as 1 liter for satisfactory analysis Improvements in microchemical methods have resulted in lowering the amount of blood necessary for analysis to volumes ranging from 10 to 30 cc In addition as has been remarked by Bassett Coons, and Salter[29] Estimations of the apparent iodine concentration of the blood—have been falling steadily for two decades—however, the reported range of normal values has become rather stable in the past few years' The methods which are relatively exact but arduous require considerable skill in the technics of analytical chemistry The information obtained however is sufficiently valuable to warrant greater clinical use

A large experience in the application of total blood iodine analyses to clinical problems by Curtis and his co workers[30, 31] by Perkin and his associates[3, 33] and by Riggs and his collaborators[34] readily demonstrated the value of total blood iodine as a measure of thyroidal function Curtis[30, 31] however after thirteen years of experience with the estimation of whole blood iodine concluded that the basal metabolic rate was more reliable as a test of thyroidal activity than the level of unfractioned whole blood iodine Riggs[34] found a sharper contrast in the values for total blood iodine of normal persons and in patients with hyperthyroidism or myxedema His normal values were lower and less variable than previous studies ranging from 2 5 to 3 7 micrograms per 100 cc in subjects who had received no iodine for at least three weeks before the analysis or who had not had a diagnostic test using an iodine containing drug

Gley and Bourcet[3] were unable to remove iodine from the blood of dogs by dialysis and therefore concluded that plasma iodine was bound to protein Modern studies have confirmed their conclusion and have shown more exactly the nature of the various fractions of iodine found in the blood

Salter and his associates[29, 36] furthered knowledge of blood iodine fractions with chemical studies of the blood and correlated these studies with clinical material The protein-bound iodine in the plasma occurred

chiefly in the albumin fraction of the blood Fluctuations in protein bound iodine were dependent upon thyroid activity Fractionation of the protein bound iodine resulted in the finding of a low rather constant level of iodine due to diiodotyrosine and a higher variable level of iodine due to thyroxine Total protein bound iodine varied largely with thyroxine secretion—it was high in thyrotoxicosis and low or absent in myxedema Inorganic iodine as contrasted with protein bound iodine was found to be low and constant in value except following iodine ingestion It was thus concluded and all subsequent observations have borne out this point that the measurement of protein bound iodine is of consider

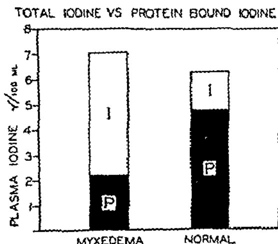


Fig Values are given for inorganic I iodine and protein I und I iodine in the plasma of two individuals Obviously unless the inorganic iodine is excluded the significant variations in P iodine may be masked From Salter W T Bassett A M and Sappington T S Protein bound iodine in blood VI Its relation to thyroid function in 100 clinical cases Am Jour Med Sci 1941 cci 527 4

able value in the study of clinical thyroid physiology as it is an index of circulating thyroid hormone and may appropriately be called hormonal iodine (Figs 3 4)

In their cases of thyrotoxicosis and myxedema exact correlations between the basal metabolic rate clinical evaluation and protein bound iodine levels in the serum were found in about two thirds of the patients A critical analysis of the case histories however clearly indicates an even higher correlation between the protein bound serum iodine level and the state of thyroid function

Riggs and his associates have contributed important studies on the effect of administered thyroid upon the protein bound iodine level in normal subjects and on the protein bound iodine concentration in the serum of patients with hyperthyroidism and myxedema[37, 38, 39] In untreated myxedema the serum iodine was characteristically subnormal or absent treatment with thyroid caused a linear elevation in the level of serum iodine in accordance with the dosage of thyroid, 65 mg (1 gr)

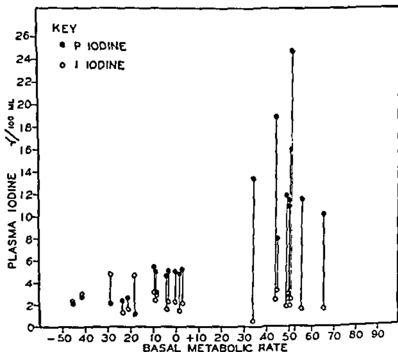


Fig 23 In cases ranging from myxedema to marked hyperthyroidism the inorganic I iodine tends to remain constant although the protein bound P iodine rises as thyroid activity increases From Bassett A M Coons A H and Salter W T Protein bound iodine in blood V Naturally occurring iodine fractions and their chemical behavior Am Jour Med Sci 1941 cciı 516 7

elevating the serum iodine by 2 micrograms per 100 cc The basal metabolic rate responded more slowly than the blood iodine levels to alteration in the thyroid state In hyperthyroidism at least 95 per cent of all cases had elevation of the protein bound serum iodine This elevation frequently declined with administration of iodides—occasionally to normal levels Following radical subtotal thyroidectomy low values often persisted permanently associated with normal metabolic rates but with slight elevations in the serum cholesterol and some clinical evidence of

mild hypothyroidism The level of the serum iodine therefore was more sensitive than the basal metabolic rate in measuring thyroid hypo*function*

When desiccated thyroid was administered to normal subjects there was far less change in the metabolic rate and protein bound serum iodine than in myxedema The administration of 0 7 to 2 0 gm (10 to 30 gr)

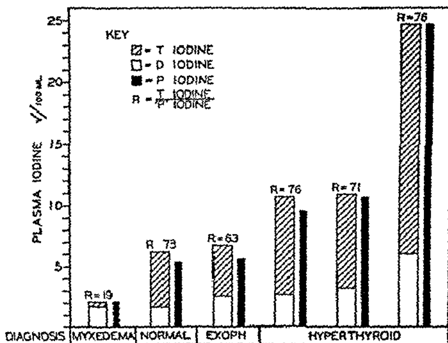


Fig 24 In cases ranging from myxedema to marked hyperthyroidism the absolute rise in protein bound P iodine is due largely to an elevated thyroxine like T fraction From Bassett A M Coons A H and Salter W T Protein bound iodine in blood V Naturally occurring iodine fractions and their chemical behavior Am Jour Med Sci 1941 cc11 516-27

of dried thyroid however caused abnormally high serum iodine levels an elevated basal metabolic rate and clinical signs of thyrotoxicosis Although the normal subject was resistant to thyroid once enough was given to raise the serum iodine the correlation between rises in that value and the basal metabolic rate was exactly the same as that in myxedematous patients Two conclusions were drawn from this study normal tissues are as sensitive to thyroid as myxedematous ones and the degradation of

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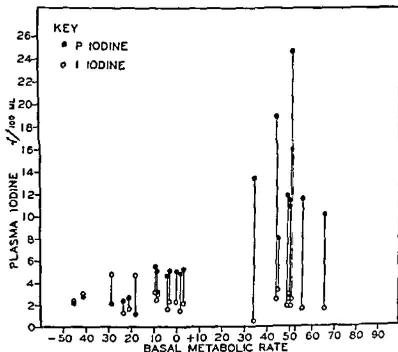


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elevating the serum iodine by - micrograms per 100 cc The basal metabolic rate responded more slowly than the blood iodine levels to alteration in the thyroid state In hyperthyroidism at least 95 per cent of all cases had elevation of the protein-bound serum iodine This elevation frequently declined with administration of iodides—occasionally to normal levels Following radical subtotal thyroidectomy low values often persisted permanently associated with normal metabolic rates but with slight elevations in the serum cholesterol and some clinical evidence of

normal iodine to inorganic iodine by the normal thyroid gland probably explains the tolerance of euthyroid subjects to large doses of thyroid. This paper[37] contains several instructive graphs showing the parallelism between precipitable serum iodine and basal metabolic rate when thyroid is administered (Figs. 25, 26, 27).

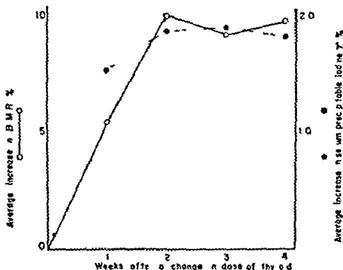


Fig. 26. Parallelism between the rate of change of serum precipitable iodine and of basal metabolic rate after an increase in thyroid dose. With increasing thyroid dosage there is almost no lag in the rise in the basal metabolism behind that of the serum iodine. This contrasts with the marked lag of basal metabolism behind serum iodine with abrupt discontinuance of thyroid medication. The increase in serum precipitable iodine or in basal metabolic rate occasioned by an increase in the dose of thyroid has been plotted against the time elapsed since the change in dose. The origin corresponds to the last value obtained while the previous dose was being administered. The points represent average values for increasing thyroid dosage in all 4 schizophrenic patients and for all increments of dose. From Riggs, D. S., Man, E. B. and Winkler, A. W.: Serum iodine of euthyroid subjects treated with desiccated thyroid, Jour. Clin. Invest. 1945, xxiv, 722-31.

Taurog and Chaikoff[40] investigated the effect of the level of daily iodine intake ranging from 1 to 480 micrograms upon the thyroxine and iodine content of the thyroid gland of rats and upon the total and protein bound iodine in the plasma. The level of the plasma protein bound iodine varied in accordance with the thyroxine content of the gland. Both were influenced by the iodine intake. An increase in iodine intake was followed by an increase in the total and thyroxine iodine

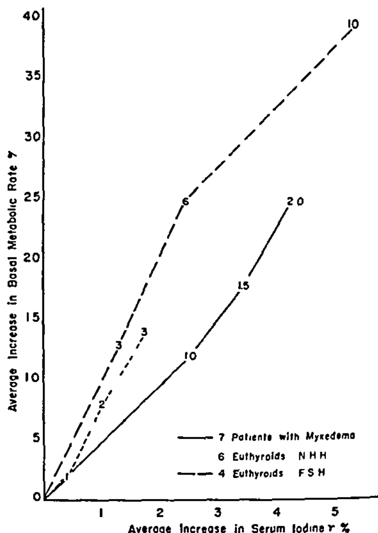


Fig 25 Relationship between the increase of serum precipitable iodine and of basal metabolic rate of myxedematous patients and of euthyroid subjects given desiccated thyroid The increase in basal metabolic rate above the average premedication level is plotted against the corresponding increase in serum precipitable iodine at various levels of thyroid dosage The dose in grains per day is indicated by the figures on the curves The curve for the patients with myxedema was calculated from data reported in a preceding paper Data from the 2 groups of euthyroid subjects reported here are plotted separately the New Haven Hospital patients being indicated by short dashes the Fairfield State Hospital patients by long dashes Each point is the average for all patients in a given group on a given dose of thyroid Note that the basal metabolic rate rises at least as much per unit increase in serum iodine in the euthyroid subjects as in those with myxedema but that a much larger dose of thyroid is required From Riggs D S, Man L B and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid Jour Clin Invest 1945 xxiv 722 31

observed up to certain levels of iodine intake beyond these levels increased intake failed to produce an elevation in the protein bound iodine (Fig 8)

Danowski and his associates[41, 4] administered inorganic iodides in both massive and small amounts to human subjects and subsequently determined the effect of iodide upon the *total protein bound and thyroxine* iodine of the blood With daily doses of 3 gm of potassium iodide over periods as long as six months elevated levels of total and precipitable

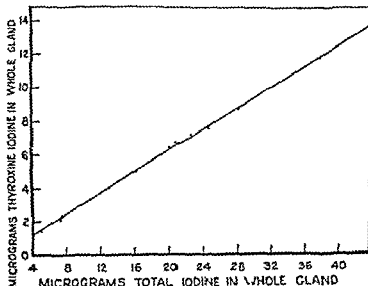


Fig 8 The relation of thyroxine iodine to total iodine in thyroid glands of rats that received varying amounts of iodine From Taurog A and Chaikoff I L *The relation of the thyroxine content of the thyroid gland and of the level of protein-bound iodine of plasma to iodine intake* Jour Biol Chem 1946 clxv 217 2

iodine occurred Total iodine levels up to 00 micrograms per 100 cc occurred the protein bound iodine rose to values of 12 to 32 micrograms except in patients with myxedema The blood thyroxine levels however did not increase during iodide therapy so that it may be inferred that the *protein bound iodine increment occurred in the non thyroxine portion*—that is in iodinated tyrosine or a related unknown substance Obviously it is not possible in patients receiving large amounts of iodides for any considerable period to utilize the protein bound iodine as an index of circulating hormone

content of the thyroid gland to a point of maximal storage beyond which increments of ingested iodine had no further effect. With maximal storage the iodine concentration in the gland was 10 000 times greater

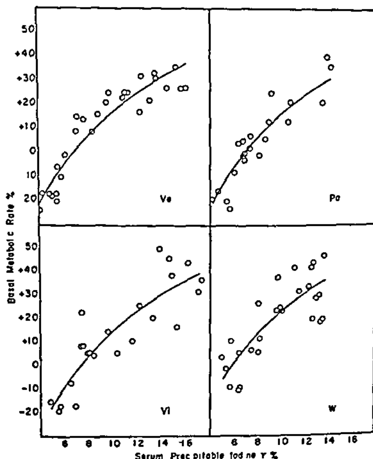


Fig 27 Correlation between serum precipitable iodine basal metabolic rate in 4 euthyroid schizophrenic patients. The points represent individual determinations of serum precipitable iodine and corresponding values of basal metabolic rate. Values determined after thyroid was discontinued are omitted for reasons discussed in the text. The solid lines are the regression curves obtained when basal metabolic rate is assumed to be a function of the logarithm of the serum precipitable iodine. From Riggs D S, Man L B and Winkler A W. Serum iodine of enthyroid subjects treated with desiccated thyroid. Jour Clin Invest., 1945 xxiv 7 31

than in plasma. The fraction of total iodine present as thyroxine in the thyroid gland remained relatively constant over the complete range of iodine intake. Increased values for protein-bound iodine of plasma were

When a tracer dose of inorganic radio iodine is injected into a normal rat upon entering the thyroid gland it is quickly converted to organic iodine so that after 24 hours a maximum of 30 per cent of the injected radio iodine has been organically bound [43] In a gland made hyperplastic with propylthiouracil all the radio iodide entering the thyroid remains inorganic and a maximum of 9 per cent of the tracer material is taken up one hour after the injection

When labeled iodide is injected into normal rats the uptake of radio iodide by the thyroid is much slower than with tracer doses so that only 2 to 5 per cent is taken up after 6 hours but it is for the most part organically bound After one hour 50 per cent of the radio iodide in the thyroid is in the inorganic fraction this is in marked contrast to the large percentages of organic radio iodine in the gland following a tracer dose [43]

In the gland made hyperplastic with propylthiouracil the uptake of radio iodide whether as tracer or labeled is similar essentially all of the

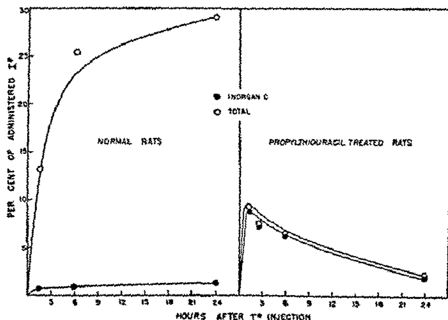


Fig 19 The uptake of a tracer dose of radioactive iodide by the thyroids of normal and propylthiouracil treated rats The latter received a diet containing 0 10 per cent propylthiouracil for 17 days From Taurog A Chaikoff I L and Feller D D The mechanism of iodine concentration by the thyroid gland its non-organic iodine binding capacity in the normal and propylthiouracil treated rats Jour Biol Chem 1947 CLXXI 189-201

Chaikoff and his co-workers[43,44] have studied further the metabolic significance of protein-bound plasma iodine by means of radioactive iodine They define protein-bound iodine as the iodine that is 'precipitated from plasma along with its proteins by such agents as tungstic acid zinc hydroxide, or acetic acid in the presence of heat and in addition cannot be freed from these proteins by simple washing' The chemical nature of this fraction needs much further clarification, as has been emphasized by Salter In Chaikoff s experiments in rats the protein bound iodine in plasma fell rapidly after thyroidectomy reaching minimal values on the third day The rate of incorporation of radio iodine into the protein-bound iodine fraction of the plasma was greatly depressed in these animals and significantly augmented in normal animals by thyrotrophin injection The conversion of injected radioactive inorganic iodine into protein bound iodine is thus proposed by Chaikoff as an index of thyroidal activity

The ten thousand fold concentration of iodine from the plasma by the thyroid gland is effected in the normal gland in part through organic binding of inorganic iodine to iodinated tyrosine and thyroxine as has been pointed out in previous discussion There is however, an additional and more significant mechanism of iodine concentration which is independent of hormonal synthesis and is referred to by Taurog Chaikoff and Feller[45] as the non-organic iodine concentrating mechanism of the thyroid In rats treated with propylthiouracil there is a complete block in the formation of organic iodine and yet the capacity of the hyperplastic glands of these animals for fixing iodine in non-organic form is greater than in the normal but is limited by the concentration of plasma iodide The iodine taken up by these glands is in the form of inorganic iodide and is not firmly bound to protein

Significant differences exist in the reaction of the normal and goitrous gland to radioactive iodine and in the response of either type of gland to tracer doses as compared with carrier or labeled doses of iodine In the tracer technique radioactivity is utilized in tracing the course of minute quantities of material through metabolic processes Labeled iodine designates ordinary iodine or iodide which is mixed with a small amount of radioactive iodine As Salter[7] has so well stated, labelled iodine is merely ordinary iodine in which one atom of (perhaps) every several million is tagged by its radioactivity Because these tagged atoms behave chemically precisely as do their fellows the investigator may assume safely that wherever he can detect one of these (perhaps) several million comrade atoms are present

become essential to the clinician and to the investigator of endocrine metabolism The ensuing explanation of the physical chemical principles involved in radioactive isotopes is based for the most part on the discussion by Buchta[4]

The modern concept of atomic structure is based upon the Bohr Rutherford theory of the atom Although the number of atoms is small the possible combinations of atoms of various elements are almost infinite at present for example over 500 000 known chemical compounds exist The undisturbed atom is electrically neutral because of the balanced *arrangement of its constituents The atom consists of three particles* the electron the proton and the neutron The electron represents the fundamental particle of negative electricity having a mass 1/2000 that of the neutron or proton The proton is the fundamental unit of positive electricity and has a charge that is the same in magnitude but opposite *in direction to that of the electron The neutron with the same mass* as the proton has no charge and is electrically neutral

Protons and neutrons make up the central core or nucleus of the atom Electrons revolve in an orbit about this nucleus The normal atom is electrically neutral because there are always as many electrons as there are protons in the nucleus Practically the entire weight or mass of the atom however resides in the nucleus The atom itself is largely space as Eddington has observed *If all the atomic nuclei and electrons of* the body were so compressed as to eliminate intra atomic and inter atomic space the resulting mass would be barely visible with a micro scope The atomic weight therefore is generally equal to the sum of the number of protons and neutrons in the atomic nucleus whereas the atomic number *corresponds to the number of electrons revolving about* the nucleus and hence is equal to the number of protons in the nucleus Thus hydrogen with one proton in the nucleus has an atomic number of one and an atomic weight of one since its nucleus contains only a single proton about which revolves a single electron Iodine with 53 pro *tons has an atomic number of 53 and an atomic weight of 1 7* because it has 74 neutrons in addition to its protons The chemical properties of a compound are determined by the number and arrangement of elec trons about the nucleus but are independent of nuclear structure except when changes in the nucleus involve changes in the arrangement of electrons

Through physical measurements it has been found that all atoms of one element or chemical species do not have the same atomic weight Though these atoms all possess the same chemical properties because of an iden

radio iodide remaining inorganic at all time intervals Maximum uptakes of 10 per cent occur within 30 minutes with a steady decline thereafter so that after 26 hours only 0 5 per cent was found

These experiments with labeled iodides have shown that the goitrous gland of a rat has a much larger than normal capacity for fixing injected iodide in non organic form (Figs 29 and 30)

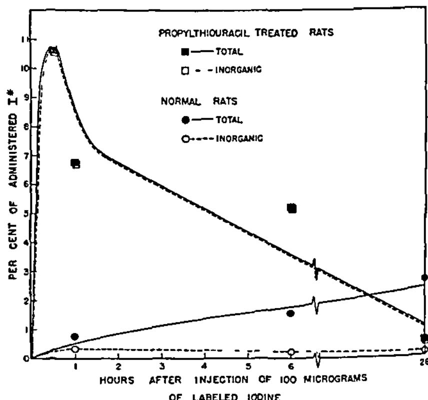


Fig 30 The uptake of 100γ of labeled iodide by the thyroids of normal and propyl thiouracil treated rats The latter received a diet containing 0 15 per cent propylthiouracil for 15 days From Taurog A Chaikoff I L and Feller D D The mechanism of iodine concentration by the thyroid gland its non organic iodine binding capacity in the normal and propylthiouracil treated rats Jour Biol Chem, 1947 CLXXI 189 201

Radioactive Iodine

The use of radioactive iodine has introduced a new and important approach to the study of thyroid physiology and pathology An under standing of the nature and utility of radioactive or tagged atoms has

become essential to the clinician and to the investigator of endocrine metabolism The ensuing explanation of the physical chemical principles involved in radioactive isotopes is based for the most part on the discussion by Buchta [46]

The modern concept of atomic structure is based upon the Bohr Rutherford theory of the atom Although the number of atoms is small the possible combinations of atoms of various elements are almost infinite at present for example over 500 000 known chemical compounds exist The undisturbed atom is electrically neutral because of the balanced arrangement of its constituents The atom consists of three particles the electron the proton and the neutron The electron represents the fundamental particle of negative electricity having a mass 1/ 000 that of the neutron or proton The proton is the fundamental unit of positive electricity and has a charge that is the same in magnitude but opposite in direction to that of the electron The neutron with the same mass as the proton has no charge and is electrically neutral

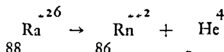
Protons and neutrons make up the central core or nucleus of the atom Electrons revolve in an orbit about this nucleus The normal atom is electrically neutral because there are always as many electrons as there are protons in the nucleus Practically the entire weight or mass of the atom however resides in the nucleus The atom itself is largely space as Eddington has observed If all the atomic nuclei and electrons of the body were so compressed as to eliminate intra atomic and inter atomic space the resulting mass would be barely visible with a micro scope The atomic weight therefore is generally equal to the sum of the number of protons and neutrons in the atomic nucleus whereas the atomic number corresponds to the number of electrons revolving about the nucleus and hence is equal to the number of protons in the nucleus Thus hydrogen with one proton in the nucleus has an atomic number of one and an atomic weight of one since its nucleus contains only a single proton about which revolves a single electron Iodine with 53 pro tons has an atomic number of 53 and an atomic weight of 127 because it has 74 neutrons in addition to its protons The chemical properties of a compound are determined by the number and arrangement of elec trons about the nucleus but are independent of nuclear structure except when changes in the nucleus involve changes in the arrangement of electrons

Through physical measurements it has been found that all atoms of one element or chemical species do not have the same atomic weight Though these atoms all possess the same chemical properties because of an iden-

tical electronic structure they vary somewhat in their atomic weights. Atoms with the same nuclear charge and electronic structure but with different atomic weights are called isotopes. Most elements have stable isotopes which are mixed in the same proportions wherever the elements occur.

The naturally occurring proportions of isotopes can be varied by special chemical or physical methods and these new percentage mixtures of isotopes may be utilized for the study of metabolic transformations by tracing the route of the isotopic element. Isotopes possessing radioactive properties lend themselves especially to this type of tracer study.

Radioactivity involves changes in the atomic nucleus with natural transmutation. These changes may occur through the disintegration of the nucleus and the emission of an alpha particle. This alpha particle is the nucleus of the helium atom. It has a high speed (12,000 to 18,000 miles per second) and large mass (over 7000 times that of an electron). The emission of the alpha particle reduces the remaining nucleus in charge and weight with the formation of two new elements thus



$$^{226}_{88}Ra \rightarrow {}^{222}_{86}Rn + {}^{4}_{2}He$$

The initial radium (Ra) atom had 88 protons and 138 neutrons with an atomic weight of 226 and disintegrated into Radon (Rn) with 86 protons and 136 neutrons and an atomic weight of 222 plus helium with 2 protons and 2 neutrons and an atomic weight of 4.

Naturally occurring radioactive elements may disintegrate in a different fashion and emit beta particles or rays. This can be illustrated by Radium E in which a neutron within its nucleus is converted into a proton and an electron. The electron is ejected and is called a beta particle. In this type of disintegration very short and penetrating gamma rays which are essentially x-rays may also be emitted. The beta rays have extremely high velocity and are less than 1/7000 the mass of an alpha particle. Since the rate of decay of radioactive elements is constant an element can be characterized by this rate. As an example given a certain number of radium atoms one half would be disintegrated after 1600 years; therefore the half life of radium is 1600 years. The half lives of radioactive substances vary from a fraction of a second to millions of years. Uranium has the longest half life of all and is most abundant.

Radioactivity is thus seen to result from instability of atomic nuclei

The stability of the nucleus is determined by the number and arrangements of its fundamental particles. Artificial or induced radioactivity was discovered in 1934 by Joliot and Curie[47] who found that radioactivity could be induced by bombarding some of the common elements such as aluminum or magnesium with alpha particles. This radioactivity persisted for some time after the bombardment ceased. All the elements have subsequently been bombarded by alpha particles, neutrons, protons or deuterons (the nuclei of heavy hydrogen) through the use of the cyclotron, which tremendously accelerates positively charged ions, and the betatron, which accelerates electrons, of the uranium pile. Radioactive isotopes can be made for any of the elements of the periodic table.

At least six radioactive isotopes of iodine have been produced and even more of them described. However I^{131} (half life 8 days) and I^{130} (half life 12.6 hours) or a mixture of both has been utilized to the greatest extent. Both can be produced by bombardment of metallic tellurium with deuterons in the cyclotron. I^{131} is also a fragment of uranium disintegration and today is available from the uranium chain reacting pile. I^{131} has completely replaced I^{130} in clinical and research applications because of its advantageous half life and ready availability.

The disintegration of most elements with induced radioactivity involves the emission of a negative or a positive electron. The positive electron, known as the positron, is produced by the conversion of a proton into a neutron and then into a positron, which has the same mass as an electron but with an opposite charge. The positron is the positive charge of the proton. This phenomenon is peculiar to induced or artificial radioactivity and has not been observed in natural radioactivity. Gamma rays may accompany disintegrations involving electrons or positrons.

The amounts of radioactive isotopes produced by bombardment are so small that they must be measured by electronic methods sensitive to radiations. Radiations can be measured by their capacity to ionize air or some other gas imprisoned between charged plates. The rate of discharge of the plates is equivalent to the number of ions formed in the air or gas and that in turn to the quantity of impinging radiation. The Geiger counter, which detects gamma rays, is commonly utilized for the purpose of measuring irradiation from I^{131}. This instrument consists of a glass tube filled with gas at low pressure, with a fine wire along its axis and a thin metal coating on the inner wall to make it electrically conductive. A high voltage (1000 volts) is produced between the wire and the wall. When an ionizing beta or gamma ray passes through the tube, ions are formed in the gas and an electrical discharge occurs under the influence

of the high voltage The current is quickly suppressed so that a pulse of current is produced for each ionizing particle This current is amplified into audible clicks whose number per minute can be used to measure radioactivity The Geiger counter itself has several disadvantages as a clinical instrument It cannot be placed in close proximity to the neck since for accuracy it must survey the entire gland at a fixed distance of 6 to 12 inches with a resultant loss in geometric efficiency In addition it is insensitive detecting only 0 1 to 1 per cent of incident gamma rays from I^{131}

The scintillation counter which can be used to detect any ionizing event is a more sensitive detector of gamma rays than the Geiger counter and is now receiving clinical application [48, 49] The scintillation or fluorescent detector measures nuclear and atomic radiations by means of a phosphor and a photomultiplier tube A phosphor is a substance that emits or can be made to emit light without sensible heat The phosphor will transform a fraction of the energy from irradiation into light emission or scintillation The photomultiplier tube will transform the phosphor scintillation into an electrical pulse which can then be amplified and recorded on a scaler or counting rate meter Various types of organic and inorganic crystal phosphors may be utilized as scintillation crystals The photomultiplier tube multiplies the emitted light quanta from the crystal The scintillation counter has proved to be from 30 to 50 times as sensitive as the Geiger counter so that tracer doses as small as 5 to 10 microcuries may be employed

It should be understood that radioactive elements behave chemically and metabolically precisely as the natural elements providing the amount is so small as to be without biologic effects from the radiation itself thus allowing their use as a convenient method for studying physiological processes In tracer work the radiation itself must be so small that it does not affect the phenomena under investigation while this can be determined only by trial a knowledge of the tissue dose is helpful Marinelli and his associates [50] consider it desirable to express the dosage in terms of roentgens since that is the unit employed with x rays and radium Dosage data for x-rays radium and radon have been satisfactorily established and can be applied to any gamma ray emitting radioactive material enclosed in a sealed container and used in the same manner as radon As most radio isotopes are ingested or injected and eventually deposited in the various tissues however to obtain accurate dosage values one must know not only the physical factors of half life and radiation energy but also the physiological factors of uptake and excretion

Use of Radioactive Iodine in the Study of Thyroid Physiology

The application of radioactive iodine to thyroid investigation has been extensively mentioned in the preceding Parts as well as in the earlier sections of this Part The thyroid whether normal or pathological cannot differentiate between ordinary and radioactive iodine its response uptake and retention of radioactive iodine has therefore served as a definite index of its reaction to ordinary iodide The radioactive iodine utilized in the great bulk of reported investigations has been I^{131} with a half life of 8.0 days This isotope emits chiefly beta rays whose action is limited to a few millimeters of tissue but with intense radiation within that area Gamma rays are also emitted which ionize negligibly within the body but which are penetrating and can be measured by an externally placed gamma ray detector such as the Geiger or scintillation counter

Hertz Roberts and Evans[1] were the first to investigate thyroid function with radioactive iodine in animals Hamilton and Soley[3] in the following year extended this method to normal and goitrous patients with and without thyrotoxicosis These authors studied both the absorption and excretion of labeled iodine as well as the total and radioactive iodine content of the thyroid gland itself Actual measurements of gamma ray emission were made by placing a Geiger counter over the thyroid gland and curves of iodine uptake were constructed The urinary excretion of radio iodine in normal persons or in goitrous subjects with normal thyroid function was found to be similar Patients with toxic nodular goiter had excretion rates that were the same as those in patients with toxic diffuse goiter In patients with myxedema the renal excretion of radio iodine was much slower than in other patients but much greater amounts were excreted Fecal excretion of radio iodine was low not over 3 per cent except in one case where it was 11.5 per cent A dose of radio iodine was detectable in the thyroid within twenty minutes after oral administration Normal subjects excreted about 80 per cent of the dose in the urine over a 5 day period most of it during the first 24 hours The thyroid gland in hyperthyroid patients who had not previously received iodides took up iodine much more rapidly than the normal gland but was unable to retain this iodine as well as the euthyroid gland

Hertz Roberts and Salter[84] in 1942 found that the thyroid glands of patients with hyperthyroidism collected 80 per cent of administered radio iodine when the associated dose of sodium iodide was less than 2 mg With larger accompanying doses of sodium iodide the percentage

collected was smaller Iodinized glands also collected smaller amounts of radio iodine

Rawson and his co workers[5 56] found that in a patient with thiocyanate induced goiter there was a small percentage excretion of tracer amounts of radio-iodine in the urine whereas in a patient with thiouracil induced goiter all of the tracer dose was excreted Patients with untreated

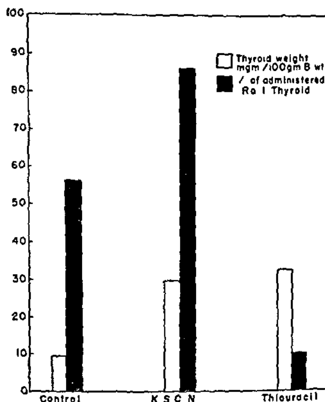


Fig 31 The collection of radioactive iodine by the thyroids of rats made goitrous by the administration of potassium thiocyanate and thiouracil The white columns represent the average thyroid weights (mg 100 gm body weight) The black columns represent the average per cent collection of administered radioactive iodine by the thyroids From Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology Jour Clin Endocrinol 1947 vii 35 6,

thyrotoxicosis excreted about 15 per cent of administered radio iodine whereas previous administration of stable iodine resulted in large excretions (Fig 31 and 32)

Hamilton, Soley, and their co-workers[57] and Leblond[58] have studied the deposition of radio iodine in the thyroid gland by the radio autographic technique The former authors found that in goitrous glands

the element was concentrated in the most active portions In normal thyroid tissue the radioactive iodine was rather evenly distributed throughout the section In non toxic goiter with or without hypothyroidism the radio iodine was found in the cellular portions but not in the colloid In hyperplastic thyroid tissue the colloid had more radio iodine than the cells of the adjacent acini apparently owing to rapid excretion by the

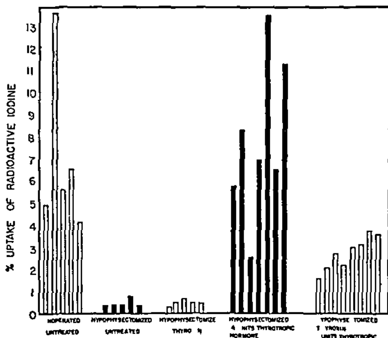


Fig 3 The effect of thyroxine on the response of the thyroid of hypophysectomized rats to thyrotropic hormone as indicated by the per cent uptake of administered radioactive iodine by the rats thyroids Each column represents the per cent uptake of radioactive iodine by a single animal s thyroid gland Twenty gamma of thyroxine were given daily for 10 days Thyrotropic hormone was given daily for the last 4 days of the experiment From Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology Jour Clin Endocrinol, 1947 vii 235-63

hyperplastic cells Leblond s results differed somewhat from those of Hamilton and his group as he found that radio iodine administered orally to patients with non toxic or toxic diffuse goiters was rapidly deposited as diiodotyrosine or thyroxine in the colloid His observations would also indicate that the radio iodine passed through the epithelium

of the thyroid cell and was deposited in the colloid as diiodotyrosine

Keating and his associates [4] have utilized tracer amounts of radio-iodine in studies of the urinary excretion of radio iodine in various thyroid conditions. The urinary excretion of radio iodine is technically simpler and more accurate than blood or tissue analysis and permits reason-

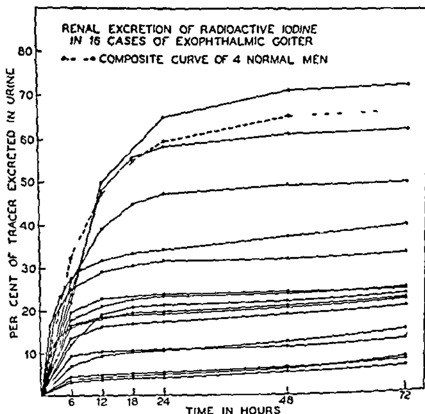


Fig 33 Urinary excretion of radio iodine in 16 cases of untreated exophthalmic goiter. The cases varied widely in clinical severity, basal metabolic rates and excretion of radio iodine. Instead of reaching a plateau, a slow and relatively constant excretion of radio iodine persists after the initial period of rapid excretion. From Keating, F R Jr, Power, M H, Berdson, J and Haines, S F. The urinary excretion of radio iodine in various thyroid states. Jour Clin Invest 1947 xxvi 1138-51

ably accurate deductions regarding the absorption of radio iodine. In euthyroid subjects from 45 to 75 per cent of the tracer was excreted in the urine within the first 48 hours, reaching a plateau at about that time with a sharply rising excretion rate during the first 24 hours. In myxedematous patients the rate of excretion was slower and the plateau was

not reached until after 4 or more days though in the end these patients excrete more radio iodine than euthyroid subjects Thyrotoxic individuals varied widely in their excretion of radio iodine In general their *excretion rates were much less than normal* but several cases with moderately severe thyrotoxicosis had excretion rates that were indistinguishable from the normal Quimby and McCune[60] studied radio iodine uptake in the thyroids of children by direct measurements over the gland after the method of Hamilton and Soley They found large

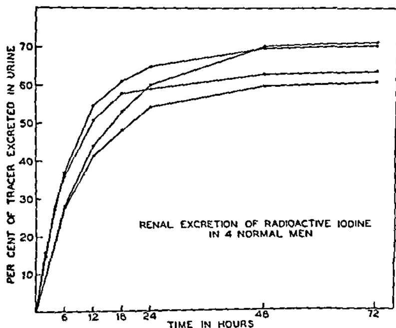


Fig 34 Urinary excretion of radio iodine in 4 normal men The form of the curves suggests an exponential function From Keating F R., Jr., Power M H Berd n J and Haines S F The urinary excretion of radio-iodine in various thyroid states Jour Clin Invest 194 xxvi 1138 5

uptakes in hyperthyroidism and low uptakes in hypothyroidism Some normal glands however had uptakes comparable to those found in myxedema The range of uptake and excretion in euthyroidism thyrotoxicosis and myxedema is such that the thyrotoxic gland may respond as a normal gland with average uptake while the action of the normal gland may be like that of the hypofunctioning gland of myxedema with minimal uptake of radio iodine (Figs 33 34 35 36)

The measurement of the excretion of radio iodine as a diagnostic method has been increasingly replaced by determination of the radio iodine uptake as more accurate methods have become available The measurement of uptake is particularly useful since it precisely determines the amount of isotope in the thyroid gland and eliminates errors due to inaccurate urine collection or adventitious temporary storage of radio

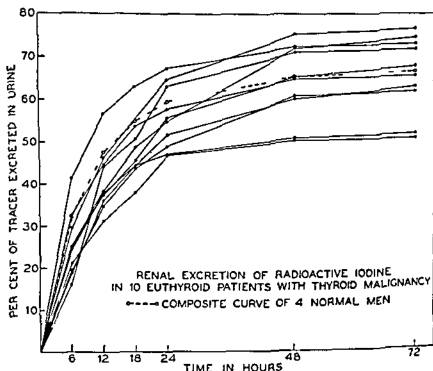


Fig 35 Urinary excretion of radio iodine in 10 euthyroid patients who had low grade thyroid malignant lesions The composite curve of the normal men is included for comparison Individual curves vary not only in the plateau that is reached but also in the time required to reach it From Keating F R Jr Power M H Berdson J and Haines S F The urinary excretion of radio iodine in various thyroid states Jour Clin Invest 1947 xxvi 1138 51

iodine in extrathyroidal tissues Radio-iodine uptake by the thyroid gland has been measured in our clinic by the four tube method devised by Freedberg[61] single Geiger tubes however, have yielded results that are no less accurate for clinical purposes[c] A sensitive method of measuring uptake is a decided advantage since the values obtained will show less overlap in euthyroid hypothyroid and hyperthyroid subjects

Keating and his associates[93] have employed four methods for measuring radio iodine accumulation in the human thyroid gland (1) measurement of the quantity of radio iodine excreted in urine within 48 hours after its administration (2) determination of extrarenal disposal rate from analysis of the curve of urinary radio iodine excretion (3) in vivo measurement of the quantity of radio iodine accumulated in the thyroid

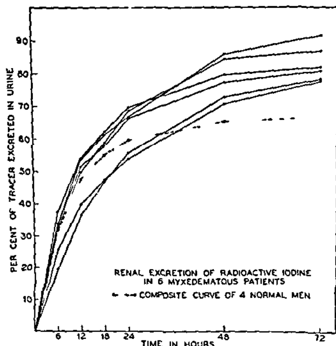


Fig 36 Urinary excretion of radio iodine in 6 patients who had myxedema The composite curve of the normal men is included for comparison Not only does more radio-iodine appear in the urine in myxedema but a much longer time is required to reach a plateau From Keating F R Jr Power M H Berdson J and Haines S F The urinary excretion of radio iodine in various thyroid states Jour Clin Invest 1947 xxvi 1138 51

24 hours after administration and (4) determination of an in vivo accumulation rate All four methods proved equally sensitive in studies of 790 patients with various conditions Extrarenal disposal rate provided the clearest picture of the state of radio-iodine function particularly in situations complicated by altered renal function In vivo observations provided more accurate information in the presence of reduced or absent

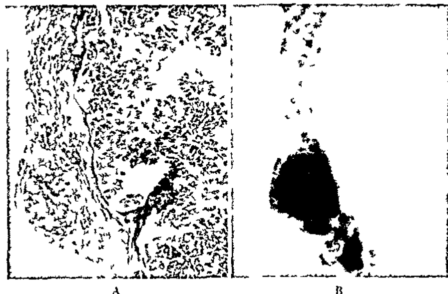
iodine accumulation than did urinary observations, but in other circumstances they were less efficient possibly owing to the intrinsic inaccuracies of in vivo measurements Determination of 48 hour urinary excretion proved a less specific measure of uncomplicated hyperthyroidism than the others and in some conditions it provided inexact and misleading information It was however the simplest and least expensive of the procedures employed

Measurement of radio iodine accumulation by any one of these methods was found highly efficient in separating more than 90 per cent of cases of exophthalmic goiter from normals Radio-iodine accumulation was significantly increased in the thyrotoxic group and strikingly reduced in patients with myxedema Discrepant results, however, were obtained in several conditions Some euthyroid patients with nodular goiter colloid goiter hyperplastic thyroid nodules and thyroid hyperplasia from antithyroidal drugs showed significant elevations of radio iodine accumulation Notable depression of radio iodine accumulation also occurred in many conditions unaccompanied by clinical hypothyroidism These included Addison s disease acute diffuse thyroiditis and Riedel s thyroiditis It was also observed for weeks to months following ingestion of inorganic iodine desiccated thyroid, and other organic iodine-containing compounds such as iodoalphionic acid (Priodax) used in roentgenography Antithyroidal goitrogenic drugs also interfered with radio iodine accumulation Normal values for radio iodine accumulation were observed in most cases of non toxic nodular goiter in about half of those with toxic nodular goiter in a few of exophthalmic goiter, and in some of myxedema Patients with Hashimoto s thyroiditis and associated clinical myxedema characteristically had normal values for radio iodine accumulation

The use of radio iodine in the study of hormone synthesis pituitary thyroid interrelations and the mode of action and assay of anti thyroidal goitrogens has been extensively described in the preceding Parts In addition radio iodine has been utilized to study the hormonal function of benign and malignant thyroid neoplasms Thyroxine labeled with radio iodine has been used by Gross and Leblond[64] to study the distribution of the hormone in various organs and tissues Radioactive thyroxine was injected into young female rats and its distribution at 2 and 4 hours in various organs measured The radioactive thyroxine quickly left the circulating blood and about one half was detectable in the gastro intestinal tract liver and pancreas within 2 hours The kidneys lungs adrenals ovaries and lymphatic tissue also showed significant amounts At

the end of 4 hours 80 per cent of the thyroxine was in the feces but the liver kidneys adrenals ovaries and lymphatic organs maintained their concentration The entrance to the gastro intestinal tract was by way of the liver and bile The pituitary gland and hypothalamus showed little or no fixation in contrast to previously reported results in rabbits

Fig 37



A B

(A) A section of low-grade papillary adenocarcinoma with clear demarcation of tumor from adjacent non-cancerous thyroid tissue At lower left is an oval area which histologically is a colloid adenoma

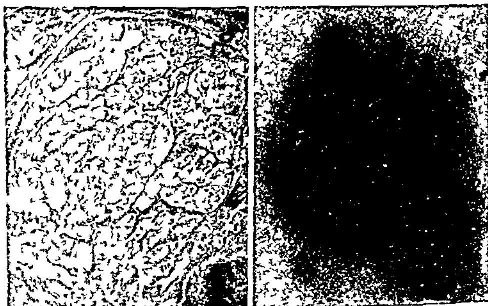
(B) The corresponding radio autograph which shows that the areas of darkening outline the non cancerous thyroid tissue There is no darkening of the plate where it was in contact with the tumor itself The oval area rich in colloid is shown to have picked up a relatively large amount of isotope as judged by degree of darkening

From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol and Rad Therap 1947 LVIII 17 32

The functional capacity of various types of benign and malignant tumors of the thyroid has been measured by their uptake of radioactive iodine Radio autography and direct counts over the thyroid gland and metastatic areas have served as the two techniques of investigation Hamilton Soley and Eichorn[65] found no deposition of iodine in thyroid

carcinoma by means of radio-autography However Frantz, Ball Keston and Palmer[66] Marinelli and his group[67 68 69] Cope and his coworkers,[70 71] and Leblond and his associates[7 73] have demonstrated that the iodine uptake of a malignant tumor depends upon the nature of the tumor The more differentiated carcinomas, especially the malignant adenomas, have a high uptake of radioactive iodine either in the thyroid itself or in distant metastases The less differentiated tumors collect radio-

Fig 38



A B

(A) A medium magnification of a solid alveolar adenocarcinoma

(B) The corresponding radio autograph showing marked retention of radioactive iodine by the tumor tissue

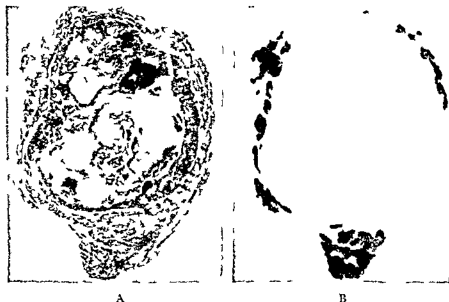
From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol., and Rad Therap 1947 LVIII 17 3

iodine in much smaller amounts or not at all About 15 per cent of all malignant tumors may be expected to take up radio iodine in some degree The benign metastasizing goiter has the highest uptake and is most susceptible to therapy with radio iodine (Figs 37 38 39)

Cope[71] by means of radioactive iodine was able definitely to establish the existence of hyperfunctioning single adenoma of the thyroid through

an avidity for tracer doses of radioactive iodine comparable to that found in ordinary toxic goiter

Fig 39



A B

(A) A Hurthle cell adenocarcinoma occupies the central portion of this section and is surrounded almost entirely by a rim of adjacent thyroid tissue The tumor itself is partly hemorrhagic and broken down

(B) The corresponding radio-autograph fails to show the deposit of any isotope in the tumor itself

From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol and Rad Therap 1947 lviii 17 32

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PART V

CLASSIFICATION OF DISEASES OF THE THYROID METHODS OF EXAMINATION OF PATIENTS WITH THYROID DISEASE

Classification of Diseases of the Thyroid

A perfect classification of disorders of the thyroid is not yet possible owing to the lack of sufficient knowledge with respect to the etiology physiology and pathology of most thyroid abnormalities The term goiter denotes enlargement of the thyroid gland whether or not the enlargement is diffuse or nodular benign or malignant or attended with symptoms and signs of increased or decreased function A simple and useful clinical classification of thyroid disease should include only those qualifying terms that are justified by the clinical picture of a given thyroid disorder The following classification has been used in our clinic and is in accord with that recommended by the American Association for the Study of Goiter

1 Non toxic diffuse goiter (iodine deficiency goiter endemic and sporadic)
2 Non toxic nodular goiter
3 Toxic diffuse goiter (exophthalmic goiter Graves disease thyrotoxicosis)
4 Toxic nodular goiter (toxic adenoma)
5 Thyroiditis (inflammatory disease of the thyroid)
    (a) acute suppurative and non suppurative
    (b) subacute or pseudotuberculous
    (c) chronic
        (1) lymphadenoid goiter (Hashimoto)
        (2) Riedel s struma
        (3) tuberculosis
        (4) syphilis
        (5) actinomycosis

(6) Echinococcus disease
(7) Chagas' disease
(8) amyloid disease

6 Thyroid deficiency
(a) cretinism
(1) endemic
(2) sporadic
(b) myxedema
(1) primary
(a) idiopathic
(b) following antithyroidal drugs radioactive iodine therapy, and thyroidectomy
(2) secondary to hypopituitarism

7 Neoplasms of the thyroid
(a) benign
(1) papilliferous adenoma or papillary cystadenoma
(2) non-papilliferous or simple adenoma
(a) the embryonal adenoma
(b) the fetal adenoma
(c) the simple adenoma
(d) the colloid adenoma
(e) the Hurthle cell adenoma
(b) malignant
(1) low malignancy
angioinvasive tumors
(a) adenoma
(b) malignant papillary cystadenoma
(2) moderate malignancy
adenocarcinoma
(a) papillary
(b) alveolar or solid
(c) Hurthle cell
(3) high malignancy
(a) carcinoma
(1) small cell (carcinoma simplex)
(2) giant cell
(3) epidermoid
(b) sarcoma
(1) fibrosarcoma
(2) lymphosarcoma

8 Thyroid anomalies
  (a) lingual goiter
  (b) lateral aberrant thyroid
  (c) thyroglossal cysts

Methods of Examination

The examination of patients with possible thyroid disease should be systematic and as in all patients should proceed from the history and physical examination to laboratory determinations of both general and specific character The features of the history that are of diagnostic usefulness may be considered in three groups

(1) symptoms of hyperfunction
(2) symptoms of hypofunction
(3) symptoms produced in surrounding structures by the goiter

In addition familial and environmental factors are frequently pertinent

The symptoms of hyperfunction are primarily due to excessive secretion of thyroid hormone These commonly present themselves as nervousness palpitation tremor weight loss dyspnea weakness increased sweating increased appetite, and diarrhea A fuller account of the symptomatology of thyrotoxicosis will be given in the Part on Toxic Diffuse Goiter Hypofunction of the thyroid manifests itself chiefly by thermophobia decreased sweating hypersomnia myxedematous swelling of the skin and face bradycardia slowness of cerebration and speech gain in weight and hoarseness Finally the thyroid enlargement may be painful and tender when it is the site of acute inflammatory disease or it may produce local pressure symptoms upon the trachea esophagus neck veins or the recurrent laryngeal nerves While excessive or deficient secretion of the thyroid hormone can generally be measured by its effect on heat production through the estimation of the metabolic rate only part of the symptoms of hyperfunction or hypofunction are related to the calorigenic activity of the thyroid Means and Lerman [1] have pointed out the extent to which the symptoms of thyroid dysfunction may be explained on the basis of alterations in the metabolic rate Marked hypermetabolism induced by dinitrophenol for example produces none of the symptoms of thyrotoxicosis Dodds and Robertson produced basal metabolic levels of 20 to 30 per cent by the administration of dinitro o cresol in patients with myxedema without any change in the clinical picture An elevated basal metabolic rate from non thyrogenous causes will not induce increased warmth or sweating or indeed tachycardia Even persons who are normal in every respect may have low metabolic

rates and yet not show any symptoms or signs of hypothyroidism

The physical examination of the patient should be supplemented by search for those features that are indicative of thyroid disorders The general appearance and manner of the patient will vary from the over active exuberant restlessness of the thyrotoxic individual to the slow, deliberate and phlegmatic character of the patient with myxedema Stature is of importance in juvenile patients since there may be an increased rate of growth in hyperthyroidism or cretinous dwarfism in hypothyroidism The nutritional status may also reflect thyroid dysfunction as well as vitamin deficiencies resulting from such dysfunction Marked obesity rarely occurs with myxedema but hyperthyroidism not infrequently produces emaciation

The facies in hyperthyroidism or myxedema are usually characteristic showing in the former instance flushed shiny and moist skin with bright staring eyes and leanness of the face In myxedema there is a general puffiness of the face with thickened and blunted features having a yellowish pallor the eyelids are puffy and the lips thickened malar flush may be observed The hair is fine and glistening in hyperthyroidism and may be prematurely grey, in hypothyroid states the hair is dry coarse and brittle, it is usually sparse over the temporal regions of the scalp and the outer portions of the eyebrows the beard grows slowly

The skin generally is pink, warm and moist in hyperthyroidism whereas it is dry scaly thickened pale, and cold in myxedema the thickening is most noticeable over the extensor surfaces subcutaneous fat pads are usually present over the wrists and in the supraclavicular and and suprascapular areas

The tongue on extension shows a fine tremor in hyperthyroidism it may be otherwise normal but frequently presents features indicative of deficiency of the B vitamins In myxedema the tongue is large overfilling the mouth is heavily coated, and shows dental impressions along its periphery on extension The voice is low pitched guttural and hoarse in myxedema with slow and halting speech but in thyrotoxicosis the speech may be rapid and dissilient

Eye changes are frequently associated with altered thyroid function but are not in themselves indicative of the state of thyroid function The changes that are commonly noted comprise exophthalmos widened palpebral fissures ocular palsies of varying degrees lid lag fatty or myxedematous swelling of the upper and lower lids as well as injection and chemosis of the conjunctivae and corneal ulcers The ocular syndromes associated with toxic goiter will be considered more elaborately

in the discussion of that disease Exophthalmos may be simulated by widening of the palpebral fissures and is best evaluated clinically by observation of the eyeball after gentle closure of the eyelids This also permits detection of incomplete closure of the palpebral aperture such as may occur during sleep in the exophthalmic patient The exact degree of exophthalmos is readily measured with the Hurthle exophthalmometer By means of mirrors this instrument can determine with considerable accuracy the degree of eyeball protrusion through measurement of the distance from the deepest part of the lateral wall of the bony orbit at or just below the frontozygmatic junction to the point of greatest convexity of the cornea

Cardiovascular changes are noteworthy when thyroid function is altered In hyperthyroidism the heart is overactive and may be dilated the rate is increased the pulse pressure widened by an increase in systolic pressure as well as a decreased diastolic pressure physiological systolic murmurs are frequent over the pulmonic and mitral areas the snapping and accentuated first sound at the apex with tachycardia may simulate a short presystolic murmur paroxysmal auricular fibrillation may be present In myxedema the heart is usually enlarged the sounds are quiet and the rate is decreased, murmurs and arrhythmias are usually absent

Neuromuscular manifestations occur frequently in thyrotoxicosis These include the usual fine rapid tremor of the extremities as well as various myopathies and muscular weakness In myxedema there may be slowness of cerebration and muscular weakness Toxic psychoses may occur in both conditions

Finally the thyroid itself should be carefully examined by inspection palpation and auscultation For inspection of the thyroid adequate illumination and complete exposure of the neck are essential The patient should be comfortably seated with the chin slightly extended and the neck muscles relaxed The thyroid region should be viewed both from in front and from the sides Normally except in thin individuals the contours of the thyroid are not apparent In pathological states various degrees of enlargement may be visible The degree of symmetry the presence of nodules or masses and enlargement of neighboring lymph glands may be readily discernible Lesser degrees of enlargement and small or deeply placed nodules may become perceptible only during swallowing This is best accomplished by having the patient swallow small mouthfuls of water while the thyroid region is under inspection In addition one should note scars telangiectacies distended neck veins and increased or abnormal pulsations

Observation of the effect of deglutition on the position and mobility of the goitrous thyroid is of great diagnostic value Nodular and diffusely enlarged thyroid glands will ordinarily move upward during swallowing This arises from the close relation between the thyroid and the larynx and the trachea which are pulled upward with swallowing With infiltrative lesions that have extended beyond the thyroid capsule and adhered to surrounding structures the upward movement on deglutition may be lost Very large goiters may appear fixed, but careful examination during swallowing will usually reveal slight movement of the larynx underneath the mass Other swellings not connected with the thyroid but attached to or arising from the larynx and trachea may also exhibit upward motion during the act of swallowing These will usually consist of rare chondromatous tumors arising from the outer surface of the larynx or more rarely lymph nodes that have become adherent to larynx or trachea Occasionally fibromas or sebaceous cysts may simulate goiter especially when there is upward movement in swallowing because of attachment to the larynx or trachea

For palpation of the thyroid satisfactory relaxation of the neck muscles may be obtained by seating the patient in a chair with high and straight back support although this is not essential in most patients Slight flexion of the neck will secure adequate relaxation of the neck muscles Because of the helpful information obtained through deglutition a glass of water should be at hand for the patient s use Though many authorities prefer to palpate the gland while standing behind the patient our experience has indicated that adequate palpation may be carried out by sitting in front of the patient Palpation yields information regarding the size and general contour of the gland its consistency, symmetry, degree of surface smoothness or nodularity, the presence of thrills and tracheal displacement A special palpatory technique is used to determine the presence of deeply placed nodules and more clearly to outline the lateral borders of the gland In this method the patient first holds a small amount of water in the mouth until requested to swallow The examiner then displaces the trachea with the thumb of one hand and grasps the opposite thyroid region with the fingers and the thumb of the other hand the latter thumb lying along the anterior border of the sternocleidomastoid muscle and the fingers approximately posterior to the thyroid lobe The patient is then asked to swallow and as swallowing occurs the thumb and fingers are brought together with the thyroid lobe and its contents pressed firmly between Pressure is constantly maintained by the opposite thumb to displace the trachea in such a manner as to force

the lobe that is undergoing examination into the examiner s grasp This maneuver is repeated with the other side Many swallows may be necessary before the examination is completed and the examiner is satisfied regarding the presence or absence of nodules their degree of mobility and their relation to deglutition In addition direct palpation of the thyroid may be achieved by displacement of the medial border of the sternocleidomastoid muscle and by fingering the surface of the exposed lobe *In some patients the neck muscles are better relaxed when* the patient is recumbent with the head of the table raised

The normal thyroid gland cannot be felt except in thin persons when it may be barely outlined as a thin layer of tissue slightly firmer in consistency than the overlying soft tissues Thyroid size can be roughly estimated as there are no really accurate clinical methods of determining its size or weight The size of discrete nodules may be approximated and stated in metric measurement Diffuse enlargement is ordinarily stated in relation to the size of the normal gland

The consistency of the goitrous gland may vary from the soft doughy character of the small colloid gland to the stony hardness of chronic thyroiditis calcification or malignancy Tenderness is present only in acute thyroiditis or following sudden hemorrhage in a thyroid cyst The hyperplastic gland of Graves disease is firm rubbery and well delineated usually with palpable thrills over the superior poles Following iodinization the hyperplastic gland hardens in consistency and the lobes may become so sharply marked as to simulate nodules Nodular goiters also vary greatly in consistency from soft cystic masses which merge into surrounding thyroid parenchyma to firm discrete swellings such as are seen with benign or malignant tumors

Symmetrical enlargement is the rule with early colloid goiters in Graves disease and in certain types of chronic thyroiditis whereas benign and malignant nodular goiters are usually asymmetrical This asymmetry frequently leads to displacement and compression of the trachea The displacement is discernible on physical examination but anteroposterior compression can be determined only by roentgenography

Palpable thrills are frequent in thyrotoxicosis and may be occasionally present in large cystic masses containing dilated blood vessels The thrill is the palpatory equivalent of systolic or systolic and diastolic murmurs which may be audible by stethoscopy over the upper poles of the thyroid gland Thrills and murmurs must be differentiated from those trans-

mitted along the carotid vessels If present they constitute supporting evidence of thyroid hyperfunction

Finally, laryngoscopic examination of the vocal cords is indicated in all thyroid patients with hoarseness voice changes stridor and dyspnea In all those patients who may be subjected to thyroidectomy, inspection of the vocal cords is obligatory, since the presence of vocal cord palsy will influence the decision on operation, the type of anesthesia, and the scope of the operation itself The need for laryngoscopy under these circumstances arises from the close anatomical relation of the recurrent laryngeal and superior laryngeal nerves to the posterior surface of the gland While thyroidectomy is the more frequent cause of injury to these nerves, thyroid disease itself may be responsible through pressure stretching, or actual infiltration of the nerves Any type of thyroid disease may cause such involvement of the nerves but malignancy and thyroiditis are more likely to do so

Roentgenographic Examination

This method of examination aids in the demonstration of the following (1) tracheal displacement compression and softening, (2) esophageal displacement, (3) calcification within the thyroid, (4) intrathoracic extensions of a cervical goiter or aberrant thyroid nodules placed within the thorax, (5) cardiac changes induced by thyrotoxicosis or hypothyroidism (6) alterations in bone associated with thyroid disease

Both anteroposterior and oblique roentgenograms are essential for the evaluations of tracheal displacement and compression caused by thyroid pathology Lateral displacement of the trachea will appear in anteroposterior view whereas compression will be more readily exhibited by an oblique view Tracheal malacia or softening of the tracheal rings may be best observed fluoroscopically by the Valsalva experiment forced expiration with the nose and mouth closed produces visible distention of the trachea at the area of softening Such softening may lead to tracheal collapse during operation and is therefore an indication for intratracheal anesthesia

Dysphagia is rarely produced by goiter, but esophageal displacement and narrowing are not uncommonly found with nodules situated between the trachea and esophagus or with intrathoracic goiter Such alterations are readily demonstrated by anteroposterior and lateral views taken during the swallowing of barium

Hardness of a thyroid nodule may be due to calcification and this can

be demonstrated only by roentgenography As a rule thyroid malignancy does not show calcification

The presence size and extent of intrathoracic or substernal goiters can be realized only by adequate roentgenologic examination of the upper thorax utilizing anteroposterior oblique and lateral views with associated barium swallows to visualize the full effect on adjacent structures

Roentgenography is also important in demonstrating the effects of increased or decreased thyroid function upon heart size and shape rhythm and amplitude of contraction In thyrotoxicosis there is usually a dilated heart with rapid forceful contraction with striking overactivity and occasionally paroxysmal fibrillation There may also be dilatation of the pulmonary conus In myxedema the heart is enlarged in all diameters assuming a pear shape with slow regular rhythm and feeble amplitude of contraction A small pericardial effusion is frequently present

Alterations in bone structure may occur in thyroid disease Long standing thyrotoxicosis in elderly patients leads to extensive osteoporosis with pathological fractures particularly in the spine In juvenile hypothyroidism on the other hand epiphyseal development is delayed and the bone age retarded Periodic roentgenographic examination of the epiphyses is particularly important in this group of patients in observing the effect of therapy with thyroid substance

Special Diagnostic Procedures in Thyroid Disease

The definitive evaluation of alterations in thyroid function depends ultimately on the employment of special laboratory procedures which have proved dependable when properly carried out and critically interpreted The special procedures include the following

(1) the measurement of the basal metabolism
( ) the determination of the protein bound or serum precipitable iodine
(3) the measurement of the uptake and excretion of a tracer dose of radioactive iodine
(4) the determination of the cholesterol content of the blood
(5) the measurement of the arm to tongue circulation time
(6) electrocardiography

Basal Metabolism in Thyroid Disease

The measurement of the basal metabolism has become the starting point in the laboratory investigation of thyroid function and its value has been repeatedly affirmed in the diagnosis of thyrotoxicosis and myx

edema. Basal metabolism actually represents the rate at which oxygen is consumed by an individual lying quietly in the morning, 12 to 14 hours after the last ingestion of food. From the oxygen consumption one can readily calculate the caloric production with a maximum error of 3.5 per cent, a degree of error of no clinical significance. The calculations rest upon the value of oxygen in terms of calories with an assumed respiratory quotient of 0.82, 1 liter of oxygen at this respiratory quotient representing caloric values of between 5.047 and 4.485 depending upon whether carbohydrate, fat, or protein is being consumed, the difference being slight so long as oxygen is measured. The measurement of carbon dioxide as a yardstick of metabolism introduces errors up to 33 per cent since 1 liter of carbon dioxide represents 5.047 calories when pure carbohydrate is burned, but 6.694 calories in the oxidation of fat. Thus all modern metabolism machines measure oxygen consumption in a given short unit of time by methods of considerable accuracy. All these methods depend upon the measurement of oxygen absorption by the subject in a closed system with the removal of expired carbon dioxide by soda lime. The circulation through the closed system is directed either by simple one-way valves or by an electric motor. The latter is not necessary for ease of breathing but does allow the use of tubing of small diameter.

The basal metabolism in health varies with age, sex and size and depends for its usefulness on correlation with normal standards of reference. The effect of age upon the basal metabolism is well established not only by the study of various age groups but, even better, by repeated determination on the same subject at yearly intervals. From the age of 2 to over 70 there is a progressive decline in the basal metabolism. During the first year of life there is a sharp rise to the peak values of infancy and the growth period, followed by a gradual decline during adult life.[3] The effect of sex upon the basal metabolism is slight but definite, females having a lower metabolism in ranges of from 4 to 10 per cent, depending upon age. In pregnancy, there is a gradual rise of 10 to [illegible]0 per cent in the basal metabolism, especially in the last trimester. This has been ascribed to the fetal participation in the total metabolism of the mother.[4,5] Marine, Cipra and Hunt[6] however, feel that there is actual thyroid hyperactivity during pregnancy, and this is validated by the finding of moderate elevations in the level of the protein bound serum iodine in the pregnant woman.[7] In this instance, however, it is impossible to assess the fetal contribution of thyroid hormone to the maternal circulation.

Basal metabolism can be measured accurately in any patient in terms of total oxygen consumption for any short period of time. This oxygen consumption can with equal accuracy be converted to heat production or caloric output. The figure thus obtained when expressed as calories per unit of time will not, however, by itself indicate whether the individual is consuming oxygen at a normal, increased or decreased rate. *It is therefore necessary to relate the caloric output to a factor that is more significant than age and sex, namely, body size. This may be accomplished by utilizing either height or weight or both.* The consensus is that basal metabolism is most closely correlated with the surface area. DuBois and DuBois[8] have derived a formula for determination of surface area from height and weight which can be accurately applied to individuals of any size or shape, regardless of bodily malformation or absence of extremities.

The correlation between surface area and basal metabolism is statistical but not causal, as has been most vigorously pointed out by Talbot and his associates.[9] Basal heat production actually depends on the amount of active protoplasmic mass and in normal persons of average height, weight and shape can be reasonably predicted by utilizing either height or weight or height and weight standards.[1, 10, 11] The surface area standards are advantageous, however, because they can be applied to subjects of unusual shape, a factor of considerable importance in endocrinological problems.

Kleiber,[7] in a *penetrating and humorous review* which deserves reading by all interested in the relation between body size and metabolic rate, has concluded that the metabolic rate is more nearly proportional to surface area than to body weight. He rejects, however, the theory that there is strict proportionality between true body surface area and metabolic rate. Body surface area, at best, is not well enough defined. Finally, he recommends reference of metabolic rate to the ¾ power of the body weight as the unit of metabolic body size on the basis of recent work on animals of all sizes and shapes indicating that metabolic rate is proportional to a given power function of body weight, since there exists a linear correlation between the logarithm of the metabolic rate and the logarithm of the body weight.

In children and adolescents the studies of Lewis, Kinsman and Iliff[13] and of Shock[14] have demonstrated that there is a smaller variation in values for normal subjects of a given sex and age if calories per square meter per hour are utilized than if height or weight figures are used. The tables for predicting the basal metabolism of normal children

between the ages of 2 and 12 inclusive, offered by Lewis and his associates, are based upon studies in 52 boys and 41 girls Shock s data are derived from studies on 50 adolescent boys and 50 adolescent girls between the ages of 11 5 and 18 The value of both these investigations lies in the fact that these small groups of children and adolescents were studied over periods of many years—longitudinal studies—in contrast to the larger series of Boothby Berkson, and Dunn[1] which involved single determinations in many subjects

TABLE II

CENTRAL TREND LINE VALUES FOR CALORIES PER HOUR PER SQUARE METER OF BODY SURFACE IN RELATION TO AGE FOR BOYS AND GIRLS BETWEEN THE AGES OF 2 AND 1 YEARS INCLUSIVE

(From Lewis *et al* *Am Jour Dis Children* 1937 LIII 348)

	Calories per Hour per Sq M			Calories per Hour per Sq M	
Age Years	*Boys*	*Girls*	*Age Years*	*Boys*	*Girls*
2 00	54 3	5 6	7 75	47 7	44 7
2 25	54 0	5 3	8.00	47 1	44 3
2 50	53 7	51 9	8 5	46 8	44 0
2 75	53.4	51 6	8 50	46 5	43 7
3.00	53 1	51 2	8 75	46	43.4
3 25	52 8	50 9	9 00	45 9	43.0
3 50	52 5	50 5	9 5	45 6	42 7
3 75	52 2	50 2	9 50	45 3	42 3
4 00	51 9	49 8	9 75	45 0	4 .0
4 25	51 6	49 5	10 00	44 7	41.6
4 50	51 3	49	10 25	44.4	41 3
4 75	51 0	48 9	10 50	44 1	40 9
5 00	50 7	48 5	10 75	43 8	40 6
5 25	50.4	48 2	11.00	43 5	40 2
5 50	50 1	47 8	11 5	43	39 9
5 75	49 8	4 5	11 50	4 9	39 5
6.00	49 5	47 1	11 75	42 6	39 2
6 25	49 2	46 8	12 00	4 3	38 8
6 50	48 9	46.4	12 5	4 0	38 5
6 75	48 6	46 1	12 50	41 7	38 1
7.00	48 3	45 7	12 75	41.4	37.8
7 25	48 0	45.4	13 00	41 1	37.4
7 50	47 7	45.0			

Our own experience extending over a period of almost two decades first with the original Aub DuBois standards[11] and later with the modifications introduced by Boothby Berkson and Dunn has indicated that these standards are too high for normal children and adolescents yielding

a high incidence of low basal metabolisms in these individuals There are not yet available entirely satisfactory standards for the younger age groups but those of Lewis Kinsman and Iliff [13] for children from through 1. years of age and of Shock [14] for children from 11 through 17 afford partly consistent and satisfactory standards for their respective age groups An inspection of the tables of Lewis *et al* and of Shock

TABLE III

CENTRAL TREND LINE VALUES FOR CALORIES PER HOUR IN RELATION TO WEIGHT FOR BOYS AND GIRLS

(From Lewis *et al* *Am Jour Dis Children* 1937 LIII 348)

	Calories per Hour			*Calories per Hour*	
Weight Kg	*Boys*	*Girls*	*Weight Kg*	*Boys*	*Girls*
12.0	29 7	28 0	4 5	44 6	4 6
12 5	30.4	29 1	2,.0	45 0	43.0
13 0	31 2	29 7	5 5	45.4	43.4
13 5	31 9	30.4	6 0	4,.8	43 8
14 0	3 ,	31.0	6 5	4' 2	44 3
14 5	33 2	31 6	27 0	46 6	44 7
15 0	33 9	32 2	27 5	47.0	45 1
15 5	34 6	3 9	8 0	47 3	45 5
16 0	35 2	33 5	28 5	4 .6	46 0
16 5	35 8	34 1	29.0	47 9	46.4
17 0	36 5	34 ,	9 5	48 2	46
17 5	37 1	35.4	30.0	48 5	47 0
18 0	37 7	36 0	30 5	48 8	
18 ,	38 3	36 6	31 0	49 1	
1) 0	38 8	37 2	31 5	49.4	
19 5	39.4	37 8	32 0	49 7	
20 0	40 0	38.4	32	49 9	
20 5	40 6	39 0	33 0	50	
21 0	41 2	39 5	33 5	50 5	
21 5	41 8	40 0	34 0	50 7	
22 0	42 3	40.4	34 5	50 9	
22 5	42 8	40 9	35.0	51 1	
23.0	43 3	4 3	35 5	51 3	
23 5	43 7	41 8	36 0	51 5	
24 0	44 1	4			

indicates considerable discrepancy at ages 1. and 13 owing to uneven increases in the latter standards at those ages For the present the safest practice is to utilize both sets of standards in those age periods where there is an overlap This is particularly important in the evaluation of hypothyroidism in hyperthyroidism the basal metabolism tends to be elevated beyond the 10 per cent introduced by shifting from one set of standards to another

TABLL IV

CENTRAL TREND LINE VALUES FOR CALORIES PER HOUR IN RELATION TO BODY SURFACE FOR BOYS AND GIRLS

(From Lewis *et al* *Am Jour Dis Children* 1937 LIII 348)

Body Surface Sq M	*Calories per Hour* *Boys*	*Girls*	*Body Surface Sq M*	*Calories per Hour* *Bo*	*Girls*
0 540	9 9	28.4	0 940	44 8	41 0
0 560	30 8	9 3	0 960	45.4	43 7
0 580	31 6	,0 1	0 980	46 0	44 3
0 600	32 5	30 9	1 000	46 6	44 9
0 6 0	33.4	31 7	1 020	47 1	45.4
0 640	34 2	32 5	1 040	47 7	45 9
0 660	35 0	33	1.060	48 2	46.4
0 680	35 8	33 9	1 080	48 8	46 9
0 ,00	36 5	34 6	1 100	49 3	47.4
0 720	37 2	35 3	1 120	49 8	47 8
0 740	37 9	36 0	1 140	50 2	48 2
0 760	38 6	36 7	1 160	50 6	48 7
0 780	39 3	37.4	1 180	51.0	49 1
0 800	40 0	38 1	1 200	51 5	49 5
0 820	40 7	38 8	1 2 0	51 9	
0 840	41.4	39 5	1 40	52 3	
0 860	4 1	40 2	1 260	52 6	
0 880	4 8	40 9	1 80	53 0	
0 900	43 5	41 6	1 300	53 2	
0 9 0	44 2	42 3			

TABLI V

AVERAGE VALUES OF BASAL METABOLISM FOR ADOLESCENTS

(From Shock N W *Am Jour Dis Children* 194 LXIV 19)

Age Years	*Calories Per Square Meter Per Hour* *Male*	*Female*	*Age,*	*Calories Per Square Meter Per Hour* *Male*	*Female*
11 5	43.6	41 7	15.0	42 8	35 7
12.0	45.0	41.0	15 5	41.4	34.4
12 5	44.4	40.4	16 0	41 1	34 2
13.0	44 1	39 9	16 5	41.0	34 6
13 5	43 2	38 8	17 0	40 9	33.4
14.0	43 5	38.0	17 5	40 6	33.4
14 5	4 9	36 5			

Many standards are available for use in adults An understanding of the bases of these standards is essential in their application in the clinic

The original standards of Aub and DuBois[16] published in 1917 are satisfactory but do not segregate the yearly decrease in metabolism demonstrated by the standards of Boothby and Sandiford[11] or of Boothby Berkson and Dunn[15] The last mentioned standards are based upon large numbers of subjects tested for the first time and are therefore particularly valuable for the exclusion of hyperthyroidism The standards of Harris and Benedict[10] were based upon repeated determination upon a small number of trained subjects yielding substantially lower values than the Aub DuBois standards or their subsequent modifications

Each physician or clinic should select the standards that are most appropriate to the group of patients under study We have employed the Aub DuBois standards as modified by Boothby Berkson and Dunn[15] with satisfactory results in adults In our clinic the range of normal with these standards has been found to be between minus o and plus 5 per cent The standards utilized in any clinic should be checked in clear cut clinical cases of hyperthyroidism and myxedema The accurate application of standards requires observation in many patients at all levels of thyroid function as well as an adequate number of tests in each patient to establish true levels of basal metabolism All this of course implies accuracy and care in the performance of the test itself

While the determination of the basal metabolic rate is probably the simplest single test of thyroid function it should be clear that there are clinical conditions with elevation or depression of the basal metabolism which have no demonstrable relation to alterations in thyroid function The following conditions frequently are associated with persistent and marked elevations of basal metabolism (1) arterial hypertension (2) chronic heart disease with or without myocardial failure (3) malignant lymphoma and chronic leukemia (4) polycythemia vera (5) pheochromocytoma (6) acromegaly Abnormally depressed rates of basal metabolism are regularly encountered in undernutrition anorexia nervosa Addison s disease and non thyrogenous hypometabolism In panhypopituitarism (Simmonds disease) the basal metabolism is always low but here there is failure of thyroid function secondary to the pituitary disease with failure of thyrotrophin production The differential diagnosis between these conditions and thyroid disease depends therefore on diagnostic procedures other than basal metabolism determination

Protein bound (Precipitable) Iodine of the Blood in the Diagnosis of Thyroid Disease

In the preceding Part the physiological significance of the protein

bound iodine of the blood was discussed, the essence of the matter being that the protein bound iodine is a measure of circulating thyroid hormone reflecting therefore the state of thyroid function This has been more conclusively demonstrated by Taurog and Chaikoff[17] who employed radioactive iodine to study the nature of the iodine contained in plasma First they demonstrated that 90 per cent of the plasma iodine behaved like thyroxine in its solubility properties, secondly by utilizing thyroxine as a carrier for radio iodine extracted from plasma they showed through repeated recrystallization that this radio iodine containing material was in the same chemical form as thyroxine and thirdly by employing immiscible solvents they found that the distribution of radio-iodine and ordinary iodine in plasma was the same

The measurement of protein bound iodine affords therefore an accurate index of circulating hormone, and since circulating hormone reflects the functional activity of the thyroid its estimation has a definitive value The amounts of iodine dealt with are small ranging from 0 5 to 35 micrograms per 100 cc of blood and require exacting and arduous methods With current methods the range of normal varies from 3 5 to 8 gamma per 100 cc of blood[18, 19, 20, 21, 22, 23] The serum protein-bound iodine is markedly depressed or absent in myxedema and cretinism and elevated in hyperthyroidism In normal pregnancy values between 6 2 and 11 [illegible] gamma per 100 cc of serum have been reported[7] This elevation occurs by the end of the first month

The determination of the protein-bound iodine combined with basal metabolism levels and the uptake of radioactive iodine represents in our opinion the most precise laboratory tests available for the evaluation of function in thyroid disease The measurement of the blood protein bound iodine has many advantages The blood sample can be drawn at any time does not require the fasting state or patient co operation as in the basal metabolism test The serum can be frozen and tested at any time or can be sent to laboratories capable of performing the test accurately It is particularly advantageous in patients in whom it is impossible to obtain an accurate or a true basal metabolic rate In congestive heart failure associated with either thyrotoxicosis or myxedema the basal metabolism will reflect a higher level of thyroid function than actually exists the precipitable blood iodine level will be diagnostically helpful In mentally disturbed or psychotic patients the determination of the blood iodine level may be the only laboratory test that can be utilized Similarly in infants and children it is especially valuable requiring minimal co-operation

The defects or disadvantages in the use of the blood protein bound iodine for diagnosis hinge upon the chemical fact that inorganic iodides administered for therapy or organic iodine containing compounds used for diagnostic roentgenography will cause an elevation in the protein bound iodine of considerable degree and for a relatively long period Danowski and his co workers [4, 5] have shown that the administration of large amounts of inorganic iodides up to 7 gm daily is associated with increased levels of the protein bound iodine The maximal levels ranged from 1 to 3 micrograms per 100 cc of serum and the elevated levels required many weeks to return to normal These rises in protein bound iodine as has already been pointed out (Part II) occurred in the non thyroxine fraction and were without metabolic effect The administration of inorganic iodide in a daily dose of 0 2 to 0 6 gm over periods up to 50 days will frequently cause elevations in the protein bound iodine to high normal or slightly hyperthyroid levels These levels will return to normal in one to two weeks after the omission of iodide

Radio opaque dyes containing organically bound iodine will elevate the protein bound iodine level for prolonged periods depending upon the dye utilized Since iodopyracet (Diodrast) is eliminated rapidly if kidney function is normal reliable values for protein bound iodine may be obtained after two weeks Iodoalphionic acid (Priodax) is more slowly excreted and reliable values for the protein bound iodine may not be obtained for at least 1 weeks Iodized oil (Lipiodol) is most troublesome since it is excreted slowly and irregularly deposits of the dye may linger in the subarachnoid space and elevate the protein bound iodine for so many months that the test is rendered impractical in patients who have received this dye [6]

Mercurial diuretics may lower the protein bound iodine of the blood for at least 24 to 48 hours depending upon the rate of excretion of the mercury This results in false low values owing to the formation of insoluble mercuric compounds that prevent distillation of the iodine in the course of chemical analysis [7]

Use of Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disease

The employment of tracer doses of radioactive iodine in the study of thyroid physiology has been discussed fully in Part II This technique yields information that is useful in the diagnosis of thyroid hyperfunction in patients with diffuse and nodular goiters and to some extent in hypo

thyroidism and certain types of thyroid malignancy, such as the highly differentiated malignant adenomas and the so called benign metastasizing goiters While radioactive iodine has been made readily available at little or no cost by the United States Government, the utilization of this substance in the diagnosis of thyroid disease is necessarily limited by the need for proper facilities and special equipment required by the method The need for protection of personnel from radioactivity imposes still further restrictions on its use

Tracer studies with radio iodine may be carried out by measurements with a single- or multitube Geiger counter placed externally over the thyroid gland or by quantitation of the urinary excretion of administered radio-iodine over a 2- or 3-day period Single-tube Geiger counters are no less accurate than the multitube counters [8] Astwood and Stanley [1] have utilized external counts over the thyroid both as an aid in the diagnosis of hyperthyroidism and as a convenient and accurate method of assaying the antithyroid action of goitrogens in humans Normal subjects gradually accumulate radio-iodine after a standard tracer dose over a period of hours reaching counts of 10 to 35 per second In thyrotoxicosis the gland rapidly takes up radio iodine reaching counts in two hours of 60 to 240 per second All of the 41 thyrotoxic patients studied had distinctly greater collections than the largest collections in normal subjects

Freedberg and his associates [30] studied thyroid function in euthyroid hyperthyroid and hypothyroid patients by means of a 4 tube method In euthyroid subjects the average 24 hour thyroid gland uptake has measured about 35 per cent with a range of 16 to 45 per cent As may be seen in Fig 40 some euthyroid patients with complicating factors will take up as much as 65 per cent and very rarely slightly more Entirely normal subjects free of goiter, congestive heart failure or any type of thyroid disease in their past history shows an average uptake that is even lower namely 29 per cent with a range of 16 to 40 per cent and rarely up to 45 per cent Euthyroid patients who have had thyroidectomy for hyperthyroidism show normal uptakes Euthyroid patients with nodular or diffuse goiter congestive heart failure and previous therapy for thyrotoxicosis with I^{131} exhibit somewhat higher values of uptake averaging 39 per cent or 10 per cent above strictly normal controls This group accounts for all the abnormally high uptakes in euthyroid patients (Fig 40)

In thyrotoxicosis the average 24 hour uptake of radio iodine is about 71 per cent When thyrotoxicosis is associated with nodular rather than

with diffuse enlargement of the thyroid gland however the average uptake is about 60 per cent In patients persistently hyperthyroid after radio iodine therapy the average uptake does not differ from that of untreated patients with toxic diffuse goiter The range of uptake in hyperthyroidism may be from 41 to 95 per cent thus overlapping in the

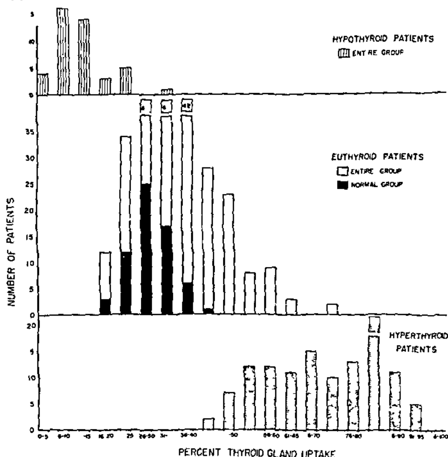


Fig 40 I131 tracer uptakes in euthyroid hyperthyroid and hypothyroid patients Reproduced from Freedberg A S Chamovitz D L and Kurland G S Metabolism, 1952 1 32

lower range that of euthyroid individuals It should be noted however that with sensitive and accurate measurement of radio iodine uptake or excretion 94 to 98 per cent of thyrotoxic patients will have uptakes over 50 per cent or excretions below 50 per cent [3, 31, 3]

In myxedema there is an average uptake of 12 per cent with a range of 0 to 25 per cent Here again, there is overlap between the hypothyroid and euthyroid patients

The various factors influencing the uptake of radio iodine by the thyroid must be noted for proper interpretation of its measurement The cause of the increased uptake in non-toxic nodular goiter is unclear since most nodules have a lower uptake of radio iodine than the perinodular thyroid tissue In congestive heart failure there is a somewhat increased uptake of radio iodine and in severe renal disease there is a decreased excretion of the isotope In both conditions impaired kidney function may be the responsible factor allowing prolonged recirculation of radio iodine and therefore an opportunity for increased pick up by the thyroid gland

Repeated administration of tracer doses of 100 to 150 microcuries of carrier-free I^{131} has no influence on uptake or turnover Ingestion of stable iodide in amounts greater than 100 micrograms will partly or completely block I^{131} uptake for as long as 3 weeks in thyrotoxic patients and 10 weeks in euthyroid subjects Stable iodide administered 3 or more days after a therapeutic dose of I^{131} in thyrotoxic and euthyroid patients without edema or congestive heart failure produces only a slight increase in urinary I^{131} with no appreciable decrease in thyroid radioactivity [31] However the administration of stable iodide to thyrotoxic patients 24 to 48 hours after a therapeutic dose of I^{131} results in considerable loss of I^{131} from the thyroid gland [30]

Organic iodine containing compounds employed in roentgenography will also block uptake of I^{131} by the thyroid gland Iodoalphionic acid (Priodax) is excreted slowly and will block uptake for as long as 8 months, whereas iodopyracet (Diodrast) will have a more transient blocking effect lasting no more than 5 days

Desiccated thyroid in therapeutic doses will depress uptake of I^{131} for many weeks In one patient uptake remained blocked for 34 weeks following thyroid administration [30, 31, 3] Potassium thiocyanate administered in doses of [illegible] gm one to one and a half hours either before or after a tracer dose of I^{131} caused considerable depression of uptake which persisted for at least one week [30] The administration of propylthiouracil will cause an increased uptake of I^{131} in thyrotoxic and euthyroid patients following the omission of the drug This increased uptake reaches a maximum 5 to 7 days after the propylthiouracil is stopped During the administration of propylthiouracil however, uptake of I^{131} is markedly depressed [30, 31, 3]

Corticotrophin (ACTH) significantly depresses radio iodine uptake by the thyroid gland with quick recovery to normal within days after omission of the hormone The effect of cortisone on I^{131} uptake is not *uniform* [32, 33, 34] *

The studies of Freedberg and his associates [32] confirm for the most part the earlier studies of Keating and his co workers [3] The latter investigators compared four methods of measuring radio iodine accumulation including (1) the measurement of the quantity of radio iodine excreted in the urine within 48 hours after its administration (2) determination of the extrarenal disposal rate from analysis of the curve of urinary radio iodine excretion (3) in vivo measurement of the quantity of radio iodine accumulated in the thyroid gland 4 hours after administration of the dose and (4) determination of an in vivo accumulation rate They found that all four methods had similar diagnostic sensitivity but that method 3 provided more accurate information in the presence of reduced or absent iodine accumulation than did method 1 whereas method proved superior in providing the clearest picture of the state of radio iodine function particularly in situations complicated by altered renal function

Myant Pochin and Goldie [3] have found the thyroid clearance rate a most sensitive and direct index of thyroid function since in all thyrotoxic patients studied it considerably exceeded the highest value observed in normal subjects They calculated the clearance as the ratio between rate of rise of thyroid content of I^{131} and the corresponding plasma concentration of radio iodine The thyroid clearance rate was thus derived from three factors each of which is altered in thyrotoxicosis (1) the average maximum count over the thyrotoxic gland was found to be three times that in controls (2) the time by which half this value was reached averaged 0 9 hours in thyrotoxicosis as against 4 5 hours in controls and (3) the plasma concentration in control subjects was

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Berson and Yalow however have evaluated the effect of cortisone on thyroid function by studies of thyroidal and renal plasma I^{131} clearance rates and for 24 hour thyroidal uptake and renal excretion measurements in 4 euthyroid subjects They found that doses of 100 mg a day or more regularly produced with but a single exception marked inhibition of the iodine accumulating function of the thyroid gland and usually produced an elevation of the renal plasma I^{131} clearance rate In almost all cases return to pre treatment levels occurred within days to a week following omission of the drug or reduction of dosage to 50 mg a day or less Under continued therapy the thyroid inhibition became progressively more marked but renal clearances tended to return toward pre treatment level in some cases (Berson S A and Yalow R S Effect of cortisone on the iodine accumulating function of the thyroid gland in euthyroid subjects, Jour Clin Endocrinol and Metabol 195 xii 407)

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Geiger Muller counter has been used to study the spatial distribution of radio iodine in the human thyroid gland[37] In the normal thyroid I^{131} is concentrated uniformly throughout the gland with the greatest concentration recorded over the middle of each lateral lobe where there is a maximum depth of tissue The directional counter is especially useful in demonstrating the presence of functioning thyroid tissue in an abnormal site or the absence of function in what is apparently thyroid tissue Thus hot nodules or hyperfunctioning nodules of the thyroid can be readily picked up by the directional counter which will show maximal iodine uptake over the site of the nodule The cold nodules or non functioning nodules will show no activity over the site of the nodule or nodules

The directional scintillation counter has proved useful in the estimation of gland size and weight and therefore in more precise determination of therapeutic doses of radio iodine[38, 39] This instrument is used to determine the count rate for a series of co ordinate points over and around the area occupied by the thyroid gland By drawing a line through the series of isocount points representing the margin of the lobes of the thyroid an outline of the gland is obtained This procedure has been greatly facilitated by the development of an automatic scanning device and a visual recorder which produce a scintigram of the thyroid gland in from 15 to 30 minutes[41] This instrument permits visual follow up of I^{131} therapy in patients with hyperthyroidism and has shown progressive decrease in size of the goiter starting in the second week following therapy with doses ranging from 2 to 12 millicuries[40] It has also proved valuable in differentiating nodules that accumulate I^{131} from those that do not and in the follow up of thyroid cancer patients where it will disclose functioning metastatic nodes before they become palpable

Quantitative measurement of the urinary excretion of radio iodine gives indirect information of its uptake by the thyroid gland Our experience with this method has been limited to patients with diffuse and nodular goiters showing either normal or increased thyroid function and has been in accord with that reported by Skanse[31] and Keating and his co workers[3] It is a less specific measure of thyroid function than measurement of thyroid gland uptake and may give inexact and misleading information

As a diagnostic procedure tracer studies have not proved as conclusive as the determination of the protein bound iodine in the blood This is due for the most part to the significant overlap among the several categories of thyroid function We agree with the following statement

about 2 5 times that in thyrotoxic patients at 1 hour after the dose These investigators feel that the thyroid clearance rate measures directly the activity of the thyroid in taking up iodine from the plasma If both the rate at which radio iodine is entering the thyroid and the simultaneous plasma concentration of radio iodine are known then the volume of plasma cleared of radio-iodine in unit time can be calculated In normal subjects about 16 milliliter of plasma are cleared of iodide per minute by the thyroid In 11 untreated thyrotoxic patients the clearance rate averaged 486 milliliter per minute with values ranging between 200 to 1400 milliliter per minute in individual patients The renal clearance rate for plasma radio iodine averaged about 30 milliliter per minute both in normal and in thyrotoxic subjects

Berson and his associates[11] have also utilized determinations of thyroidal and renal plasma I^{131} clearance rates as a routine diagnostic test of thyroid dysfunction These investigators employed a simple method of obtaining the thyroidal and renal plasma iodide clearances without the necessity of performing analyses of blood samples The method is based on an observed relationship of relative constancy between the body weight and the space of I^{131} dilution during the first half hour following intravenous administration of the isotope The clearance rates were readily determined in a single 35-minute sitting from the assay of radio activity in the neck and in a single urine specimen The clearance rates and the 24 hour thyroid uptake and renal excretion values for 87 euthyroid 18 untreated hyperthyroid 5 treated hyperthyroid and 5 hypothyroid patients were quite in accord with those obtained by the Mayo Clinic group[3] and by Myant and his associates[35] with their more elaborate methods The lowest thyroidal clearance rate in hyperthyroidism was almost twice the highest rate in euthyroidism Nevertheless overlaps between euthyroid and hyperthyroid 24 hour values occurred in about 7 per cent of normal subjects who showed clearance rates in the hyperthyroid range *

The application of newer and more precise tools has greatly aided the diagnosis of thyroid function by means of radio-iodine The directional

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Kriss has studied thyroid uptake of radio iodine after intravenous administration of 40 to 100 microcuries of carrier free I^{131} in euthyroid subjects and in patients with various thyroid disorders The uptake one hour after administration of the tracer dose exhibited excellent correlation with the degree of clinical thyrotoxicosis This method appeared more advantageous than the 24 hour oral method in that it was more rapid and accurate reducing the overlap in values between euthyroid and hyperthyroid patients (Kriss J P Uptake of I^{131} after intravenous tracer doses Jour Clin Endocrinol 1951 xi 289)

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of Keating and his associates [39] "Measurement of radioiodine accumulation is considered to be comparable but not superior to determination of basal metabolic rate as a measure of thyroid function It appears likely that it will supplement rather than supplant other diagnostic aids

Blood Cholesterol in the Diagnosis of Thyroid Disorders

The role of the thyroid in fat metabolism has been discussed in Part I Diagnostic alterations in all of the lipid constituents of the blood except the neutral fat content may occur in both hyperthyroidism and hypothyroidism These alterations occur primarily in the serum with slight changes in the lipid values of the cells Hyperthyroidism tends to lower the blood cholesterol and hypothyroidism more consistently elevates the blood cholesterol Because of the wide range of normal values significant shifts in the blood lipid values may not be appreciated until the establishment of euthyroidism returns the lipid content to values normal for the individual Patients with normally high or normally low cholesterol content of the blood will show more striking elevations in myxedema or depressed values in thyrotoxicosis than patients with average normal values [41] The wide range of normal values from 150 to 250 mg per 100 cc may obscure significant changes due to thyroid disease except as they change with amelioration of abnormal thyroid function Other diseases that alter the blood cholesterol may co exist with thyrotoxicosis and obscure the blood changes, this is especially true in diabetes and nephritis

Measurement of the Circulation Time in Thyroid Disease

The velocity of blood flow is significantly increased in thyrotoxicosis and decreased in myxedema so that its measurement affords diagnostic information about the state of thyroid function in the absence of other influencing conditions such as anemia heart failure polycythemia and fever The speed of circulation time at different levels of thyroid function is a reflection of the metabolic demands of the body increasing with thyrotoxicosis and slowing with myxedema [42, 43] Calcium gluconate [44] and sodium dehydrocholate [4] have been found useful for the clinical determination of the circulation time With these substances arm to tongue circulation time in the normal averages 12 5 to 15 seconds In thyrotoxicosis it may be as rapid as 7 seconds but averages about 8 5 seconds In myxedema it is usually prolonged to between 5 and 30 seconds

Electrocardiogram in the Diagnosis of Thyroid Function

The preceding tests have demonstrated changes that were relatively specific in measuring the level of thyroid function Electrocardiography however is of diagnostic value only in hypothyroidism and in this condition it is likewise useful as an indicator of the response to thyroid medication Specific changes have been shown to occur in leads 1 - 3 and CF4 no adequate study has yet been reported of changes in unipolar limb or precordial leads In myxedema the electrocardiogram shows a strikingly low voltage in all complexes slight prolongation of the P R interval and lowering flattening or inversion of the T wave[46 47 48] Q wave changes such as occur in myocardial infarction have not been reported These changes are completely reversible following the administration of thyroid medication In thyrotoxicosis the electrocardiogram may show tachycardia or auricular fibrillation but no changes specifically diagnostic of increased thyroid function

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PART VI

NON-TOXIC GOITER

I NON TOXIC DIFFUSE GOITER

II NON TOXIC NODULAR GOITER

III INTRATHORACIC GOITER

I NON TOXIC DIFFUSE GOITER

Introduction

Definition A diffuse and symmetrical enlargement of the thyroid generally associated with normal thyroid function occurring in either sporadic or endemic form

Synonyms Simple goiter endemic goiter colloid goiter adolescent goiter iodine deficiency goiter

Historical This disease has been recognized and described for over 2 000 years It is mentioned in the writings of Celsus Pliny Vitruvius Juvenal Aetius of Amida Roger of Palermo Marco Polo and Paracelsus A comprehensive account of the thyroid gland in medical history has been published by Iason [1]

Distribution and Incidence

Geographic distribution is the most striking aspect of this thyroid disorder It is found endemically in old glacial areas and in the great mountainous *regions* of the world where practically the entire population—animal as well as human—is affected In such districts the incidence of goiter is frequently inversely proportional to the iodine content of the water soil and air It appears at birth or in early childhood in endemic areas and at puberty or during adolescence in non endemic regions There is little or no sex difference in endemic areas but in non

goiter regions the sex ratio is 7 or 8 to 1 in favor of the female The peak of incidence is earlier by two or three years in boys than in girls, in both goitrous and non goitrous districts

The geographical incidence is of considerable interest because it has given rise to several theories concerning the pathogenesis of this type of goiter In North America the goitrous areas as revealed by thyroid surveys, comprise the Great Lakes region especially Michigan and Wisconsin the states of the northern Pacific coast, and the upper valley of the Mississippi River The North Atlantic states Maryland the South Atlantic states and those extending along the Gulf of Mexico through Texas and New Mexico have a minimal incidence of goiter In South America goiter is prevalent in the Andes and the Cordilleras In Europe the highest incidence is found in the Alps and the Pyrenees In England the highest incidence is in the Thames Valley and Derbyshire In Asia the Himalayas Caucasus Ural Altai and Japanese mountains contain areas of high goitrous incidence The oases of the Sahara the Sierra Leone, Egypt parts of the Congo and the Abyssinian Mountains represent the goitrous regions of Africa New Zealand Madagascar Ceylon Borneo Sumatra and Java all have areas of endemic goiter

Although endemic goiter is found in the mountains in the deserts and along the sea coast the percentage of the population affected in such regions as the Swiss Alps and the Himalayas is far higher than in any part of the United States or Great Britain McCarrison found a 100 per cent incidence in parts of the Gilgit district of India and Wegelin[3] could find no normal thyroid gland in autopsies in Berne Switzerland All surveys and all investigators have found great paradoxes in the geographical incidence Valleys in close proximity, served by the same watershed may have a striking difference in goiter incidence Even non goitrous Massachusetts has been found to have areas of endemic goiter in Berkshire County[4]

Etiology

Chatin[5,6,7] in a series of investigations beginning in 1850 carried out extensive analyses of the iodine content of air water soil plants and animals and concluded that iodine deficiency was the principal cause of goiter and cretinism On the basis of these findings he suggested that endemic goiter could be prevented by iodination of the water supply A commission of the French Academy after an investigation of Chatin's reports found itself unable to accept his conclusions about etiology and

recommendations for prophylaxis Since then numerous investigators particularly McClendon[8] in the United States Von Fellenberg[9, 10] in Switzerland and Hercus[11, 12, 13] in New Zealand have attempted to show that endemic goiter is caused in the first instance by an absolute deficiency in iodine content of the environment—air water soil and food The evidence for this point of view depends upon a correlation of iodine analyses involving parts of iodine per hundred billion parts of water with the incidence of goiter as found by physical examination of army recruits school children and in some instances more wide spread sampling of the population The difficulties in this type of study are apparent On the one hand there is considerable evidence of the inaccuracies of the methods used for iodine analysis and on the other hand a uniform clinical evaluation of goiter incidence is not simple Aside from these difficulties there are important exceptions to the alleged relation of goiter incidence to exogenous iodine deficiency These exceptions in turn in many instances also depend upon inaccurate iodine analyses or inadequate clinical evaluation of goiter incidence

Ucko[14] and Greenwald[15] have again called attention to the weak support lent to the iodine lack theory of goiter causation by water soil and food analyses Ucko points out that this theory is concerned with two distinct problems (1) Is an inadequate supply of iodine to the thyroid gland the immediate cause of goiter (2) If so are goitrous districts insufficiently iodinized and is this the cause of a deficient iodine supply to the thyroid gland Regarding the first question most investigators agree that lack of iodine plays a significant part in the pathogenesis of goiter but the role of other causative agents requires further study The occurrence of sporadic as well as endemic goiter and the difference in the morphology of goiters from mountainous and non mountainous regions suggest that there may be more than one causative factor The recent knowledge of goitrogenesis obtained from the study of goitrogenic agents in plants and thiourea derivatives (see Part III) certainly is in accord with such a probability Some of these agents clearly owe their goitrogenic effect to interference with the utilization of iodine by the thyroid gland and thus produce a conditioned iodine deficiency However animal experiments with iodine poor diets with attempts to prevent this dietary goiter by addition of small doses of iodine have not given conclusive results Moreover goiter can be produced experimentally by a variety of factors such as exposure to cold high protein or fat diet starvation and excess of calcium intake Hellwig[16, 17] and Thompson[18] have demonstrated that iodine poor diets pro

duce goiter more readily when they contain an excess of calcium and that iodine deficiency alone is followed often by atrophy of the gland McClendon and Foster[10] in a carefully controlled experiment, have produced goiter in a small number of rats fed iodine free diets derived from nutrients grown by hydroponics and concluded that goiter can be produced solely by iodine-lack

Critical study of the available evidence makes clear that multiple factors are involved in the causation of endemic and sporadic goiter Purely exogenous or a conditioned endogenous iodine deficiency may prove to be the ultimate cause but the definitive etiology is still unsettled

The existence of iodine deficiency in goitrous regions and its relation to goitrogenesis is likewise not well substantiated, according to Ucko[11] The methods used for iodine analysis of food, soil and water proved unreliable and yielded answers that were not reproducible in the hands of experienced chemists The estimation of goiter incidence was similarly inaccurate The criteria used were variable and observers frequently disagreed by large percentages about the incidence in the same locality Furthermore endemic goiter has occurred in iodine rich areas with endemic foci near the sea and a high iodinization of the environment Moreover there is lacking an adequately inverse relation between goiter incidence and iodinization in many areas

McCarrison[9] Blacklock[1] and Chagas have claimed that goiter is of infectious origin but this point of view has gained few adherents McCarrison, himself has stressed a low iodine intake as essential for the production of goiter through either water pollution or other noxious agents

Pathology

In Part IV, the relation of thyroid morphology to iodine metabolism has been extensively discussed In non-toxic diffuse goiter the essential pathology varies considerably but the changes involved are closely analogous to those observed in the experimental animal following the administration of thyrotrophin iodine deprivation or treatment with the antithyroidal goitrogens The pathological changes follow the Marine cycle of hyperplasia involution with atrophy as a final stage in cases where the demand for hormone is unduly intense and prolonged without adequate iodine availability Regardless of the over all picture of any thyroid gland detailed examination will usually disclose areas of pathology ranging from hyperplasia to involution

In endemic or sporadic goiter the gland is soft and diffusely enlarged The cut surface appears pale pink and slightly translucent because of its colloid content The connective tissue stroma is considerably increased giving rise frequently to pseudo lobulation The histologic appearance will vary according to the age of the goiter its stage of involution, and the geographical region of its origin and evolution Typically the acini vary greatly in size are lined with a flat epithelium and are filled with dense colloid Blood vessels are scarce or compressed by the overfilled acini Scattered areas of hyperplasia may be observed Early lobulation surrounded by thickened stroma may also be observed The geographical pathology is important because the histology of goiters arising in areas of high endemicity such as Switzerland and the Himalayas as well as that of congenital goiters in these regions differs strikingly from the histology of colloid goiters of North America or England The typical histology in the former areas consists of goiter due to increased epitheleal hyperplasia without important colloid deposits The gland is firm large and somewhat vascular with a pale fleshy appearance The acini are greatly increased containing little or no colloid the cells tend to be columnar and there may be papillary infoldings as in thyrotoxicosis It is therefore called a parenchymatous goiter With age it becomes converted into the usual colloid or nodular goiter rarely appearing after puberty This type of goiter is frequently associated with subnormal thyroid function or cretinism despite the histological picture of intense hyperplasia

Symptoms and Signs

This form of goiter is generally asymptomatic In non goitrous regions, its presence may be unnoticed by the patient until observed by others or by the physician In endemic areas the goiter is usually larger and the patient is more frequently aware of its existence The production of symptoms depends upon the size consistency rate of growth and degree of intrathoracic extension Very large goiters may produce exertional dyspnoea through compression of the trachea especially the more readily compressible trachea of children and young adults Rapid growth may similarly produce dyspnoea Spasmodic non productive cough stridor hoarseness and dysphagia are seen only with intrathoracic extension Rarely bradycardia and syncope may result from pressure of the goiter upon the carotid sinus

On examination, the thyroid is found to be diffusely enlarged in varying degree with ill defined borders The consistence of the goiter likewise varies from soft to firm and tense but never hard with a smooth surface except in the case of large long-standing goiters where a lobulated surface may be felt Thrills and murmurs over the surface of these glands are rarely encountered Intrathoracic extension may produce distention of the neck veins but this degree of extension very rarely occurs in this type of goiter

In the vast majority of cases thyroid function remains normal but occasionally failure of adequate hormone production may occur In such instances the clinical and laboratory findings of hypothyroidism will be present

Clinical Course

In endemic regions the goiter first appears in early childhood more frequently in girls than in boys whereas in non goitrous districts it is not seen until puberty and is again much more common in girls In these latter districts diffuse thyroid enlargement may appear only during pregnancy in a considerable number of cases Once the goiter has developed it may slowly regress and disappear or it may remain unaltered Increase in size and the development of nodules usually occurs in the third or fourth decade of life This is particularly true of long standing goiters The nodules in turn may remain stationary or increase in size but they rarely regress The development of hyperthyroidism in this type of goiter is exceedingly rare Pregnancy may increase the size of an existent goiter with incomplete recession after parturition

Diagnosis

The diagnosis depends upon the finding of a diffuse soft symmetrical enlargement of the thyroid without associated clinical or laboratory signs of hyperthyroidism When this type of goiter occurs in individuals with neurocirculatory asthenia or with rheumatic heart disease there may be a simulation of thyrotoxicosis In the first instance there may be present an elevation of the systolic blood pressure tachycardia tremor and sweating with a history of nervousness and palpitation In the second instance there may be a history of palpitation and dyspnoea in association with a hyperactive heart In these instances the diagnosis can

be made secure by repeated observation of the basal metabolism. Measurement of the protein bound iodine in the serum is particularly conclusive. If this facility is lacking a diagnostic test with iodide medication for a period of 10 to 14 days will usually be helpful.

Measurement of the uptake of radioactive iodine is not diagnostic as uptakes in the thyrotoxic range may occur because of the iodine avidity of these goiters. Stanbury and his associates [3] have found extremely high uptakes in the endemic goiter of the Andes region of Argentina. These patients were all euthyroid. Large colloid goiters in non endemic areas often demonstrate an uptake of radioactive iodine well beyond the average normal of euthyroidism though not so high as in the areas of goiter endemicity.

In patients with large asymptomatic goiters regardless of size and especially in patients with cough or hoarseness roentgenography of the chest in both antero posterior and oblique views as well as laryngeal examination is essential for the demonstration or tracheal deviation and compression or recurrent laryngeal nerve injury.

Prophylaxis and Treatment

Non toxic diffuse goiter is more readily prevented than cured. This simple type of goiter is by itself not serious but its sequelae in the form of endemic cretinism thyrotoxicosis and thyroid malignancy have given rise to public health problems of world wide scope. Regardless of the ultimate cause of endemic and sporadic goiter there is agreement that the thyroid gland will maintain a normal structure and function if an adequate supply of iodine is available to it. The brilliant results of the prophylaxis of endemic goiter in man through the supply of adequate amounts of exogenous iodine date back to the work of Marine and Kimball in 1917. [4] These workers after a trial of several methods of supplying adequate environmental iodine concluded that iodized table salt offered an inexpensive effective and practical means of achieving satisfactory prevention of endemic goiter. In a recent re evaluation of the subject by Kimball he concludes that the persistent use of iodized table salt will cause highly significant reductions in the incidence of goiters in school children. For instance a survey of over 61 000 children in Grand Rapids Michigan showed a decrease of goiter from 38 6 per cent in 19 4 to 8 2 per cent in 1936. In other communities in Michigan and Ohio the use of iodized salt has been regularly followed by similar decreases in the incidence of goiter.

Wegelin [6] describes the results of the campaign against goiter in Switzerland Prophylaxis by the use of iodized table salt was begun in the years 1922 to 1924 The use of this salt was gradually made obligatory in an increasing number of Swiss cantons Examination of the thyroid gland at birth for goiter, a sensitive index of the efficacy of iodine

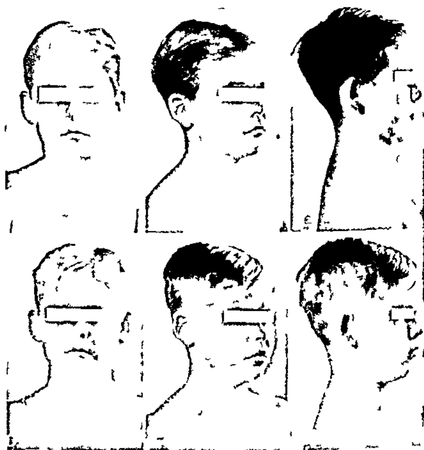


Fig 41 Case 4 J L E a boy 11 years of age with diffuse non toxic goiter A shows the goiter before oral administration of thyroid B semiprofile view C, profile view D after eight weeks of treatment with 3 grains (0 120 gm) thyroid per day note disappearance of the goiter E, semiprofile view F profile view From Rienhoff W F, Jr Arch Surg 1940 xli 487

prophylaxis has shown an increasingly higher proportion of normal glands Cogenital goiter has largely disappeared and even the percentage of glands showing minimal enlargement has decreased from 70 per cent to 7 per cent

The amount of potassium iodide used in table salt has varied from 1 part per 100 000 to 1 part per 200 000 Too large quantities of iodide do indeed increase the likelihood of iodism but there is now substantial evidence that *Jod Basedowismus—i e induction of thyrotoxicosis in nodular goiter by iodides—is essentially nonexistent*

The treatment of diffuse non toxic goiter is best accomplished by the use of desiccated thyroid (U S P) in daily dosage of 60 to 180 mg Physiologically the administration of thyroid hormone will reduce thyrotrophin secretion—an all important factor in the production and maintenance of hyperplasia of the thyroid the invariable early stage of colloid goiter In addition it supplies the body with adequate thyroid hormone exogenously allaying the demands of the organism upon its own thyroid Rienhoff [7] has demonstrated the effect of thyroid extract *in the production of atrophy of the thyroid gland in man through serial biopsies Rapid regression of the goiter over a period of weeks or months* has occurred in many instances We ourselves have regularly observed this effect in diffuse goiters The use of iodides has proved valuable in occasional cases only though they can be used without fear of the production of hyperthyroidism Iodides may best be utilized in the form of potassium iodide in saturated solution or as compound solution of iodine (Lugol s solution) in daily doses of 5 drops (Fig 41)

Treatment with either thyroid extract or iodides should be continued for months and even years after the goiter has regressed in order to *prevent recurrence*

Subtotal thyroidectomy is indicated when pressure symptoms and signs are present or for cosmetic reasons when the goiter is large and disfiguring

II NON TOXIC NODULAR GOITER

INTRODUCTION

Definition An irregular enlargement of the thyroid gland containing one or more discrete nodules and usually associated with euthyroid function

Synonyms Adenomatous goiter struma nodosa adenomatosis of the thyroid

Distribution and Incidence

Nodular goiter occurs with greatest frequency in areas of high endemicity in somewhat later age groups than those in which diffuse goiter appears being particularly common after the age of 30 This later age incidence is due to the fact that most nodular goiters evolve from preexistent diffuse colloid goiters The relative frequency at autopsy of nodular goiter in endemic and non endemic districts has been quite extensively reported in Europe [28, 29, 30] but has received inadequate attention in America Rice [31] studied the incidence of thyroid nodules in Minnesota, a goitrous region while Schlesinger, Gargill and Saxe [3] reported on the incidence in routine autopsies in three teaching hospitals in Boston Massachusetts, a non goitrous region Rice s series was smaller than that of the latter authors comprising only 390 autopsied cases as contrasted with 1373 from the Boston hospitals Both series were based on the incidence of macroscopic nodules In Minnesota, nodules occurred in about 57 per cent of autopsies whereas in Boston the average incidence was found to be about 8 per cent In both districts there was increasing incidence with advancing age so that in the goitrous area in persons between 70 and 75 years of age 100 per cent of the thyroids contained nodules In Boston nodules were twice as common in women and in those over the age of 50 the incidence approached 40 per cent

Etiology

Nodular goiter is generally regarded as a result of long continued goitrogenic influences particularly iodine deficiency This form of goiter is abundant in endemic regions especially in persons who have previously had diffuse non-toxic goiter Its incidence is markedly reduced by goiter prophylaxis Nevertheless, this is not the whole story for adenomatous goiter is frequently seen in individuals who have never resided in goitrous areas and who have never had a colloid goiter A small number of nodular goiters will represent various types of benign or malignant neoplasms The etiology of this latter group is not necessarily related to the problem of the genesis of the usual nodular goiter

The production of nodular goiter in the experimental animal was first reported by Wegelin [33] and Hellwig [34] who noted the development of thyroid adenomata and occasionally metastasizing thyroid carcinoma and sarcoma in rats kept on diets that produced a persistent hyperplasia of the thyroid Griesbach and his associates [3] found that prolonged

and continuous thyroid hyperplasia produced by the goitrogens in Brassica seeds led to the formation of thyroid nodules in the rat whereas intermittent cycles of hyperplasia and involution did not lead to colloid or nodular goiter in that animal thus affording no support to the hypothesis of Marine[31] Griesbach concluded that nodular goiter was due to long continued stimulation of the thyroid by thyrotrophin The pituitary glands of these rats all showed varying degrees of overactivity particularly evidenced by changes in the basophil cells these cells had previously been demonstrated by these workers to be responsible for thyrotrophin production Kuzell and his associates[37] have also found a high incidence of nodular hyperplasia of the thyroid in rats maintained for prolonged periods on high intakes of thiouracil

Pathology

The macroscopic appearance of nodular goiter varies greatly The nodules may be single or multiple tending to be solitary in areas of sporadic goiter and multiple in endemic regions The degree of capsule formation the amount of connective tissue and the presence of calcification will depend upon the duration of the goiter Capsulation is well marked with larger or long standing nodules but poorly encapsulated multiple nodules of small size may give rise to very large goiters The color of the nodules may likewise vary from the pale yellowish pink semi translucent character of a colloid nodule to the grayish pale and opaque appearance of the fetal adenoma Degenerative changes namely hemorrhage cyst formation and foci of calcification are particularly characteristic of nodular goiter and are more common in those of large size and among the fetal adenomas With hemorrhage various shades of red brown or yellow may appear in the nodule Cyst formation occurs through dissolution of the follicles and the cystic contents may comprise remnants of the alveolar tissue clear or gelatinous colloid material and cholesterol crystals

Histologically nodular goiter most frequently will appear either as colloid nodules or as so called fetal adenomas Definite tumors of a benign or malignant nature may present themselves clinically as nodular goiter the macroscopic structure of these nodules will be considered in the section on thyroid neoplasms The colloid nodule consists of a poorly defined fibrous capsule containing colloid filled acini often of huge size and lined by low cuboidal epithelial cells which may be so

flattened as to resemble endothelial cells The follicles toward the periphery of the nodule tend to be smaller than those in the center The smaller follicles may be devoid of colloid Focal hyperplasia of the epithelium is often present

The fetal adenoma was first described by Wolfler [8] in 1883 and was so named because of his belief that it arose from fetal cell rests This term *has persisted as a name for a definite pathological picture even though its* conceptual basis has been shown erroneous Histologically, such a nodule will show a thin capsule containing colloid and is lined by atrophic epithelium Scattered lymphocytes may appear in the interstitial tissue The nodule is composed primarily of small acini most of them containing colloid and is lined by cuboidal epithelium The acini are widely separated by a loose reticular structure whose meshwork is filled with a pale homogenous pink staining matrix which resembles intrafollicular colloid in its staining characteristics Connective tissue is typically absent

The fetal adenoma bears a close relation to the colloid nodule Rienhoff [31] after a study of wax models of the thyroid gland in correlation with stained serial sections concludes that the so called fetal adenoma is an example of extreme involutional change Boyd [40] makes no fundamental distinction between the colloid and fetal types of adenoma finding that one type shades off into the other and that in a single section both forms may appear The acini of the fetal adenoma may show active budding but no intra acinar projections Finally Murphy and Ahlnquist [41] have demonstrated the histological origin of fetal adenomas from epithelial proliferations within a colloid follicle or body of varying size and without obligate capsulation They ascribe the unusual appearance to the fact that there is intra-acinous proliferation of epithelium into the colloid which supports its growth and obviates the need for connective-tissue support

The future development of this type of lesion may be along one of these courses (1) the acini may function as normal thyroid cells (2) hyperplastic changes may occur with the formation of nodular hyperplastic and hyperfunctioning goiter (3) neoplastic change may develop (4) hemorrhage with secondary necrosis cyst formation or fibrosis may take place

The functional behavior of thyroid nodules has been clarified by Puppel Leblond and by Curtis [4] through study of radioactive iodine and ordinary iodine fractionation in thyroid nodules and in the surrounding thyroid parenchyma These investigators correlated the clinical and pathological picture of nodular goiter with the iodine and radio iodine

fractionation in the nodule and in the perinodular thyroid tissue The iodine fractions were determined as inorganic iodine diiodotyrosine and thyroxine The nodules varied in their histological picture from colloid nodule to fetal adenoma These nodules produced much smaller amounts of physiologically active organic iodine compounds than the surrounding thyroid confirming Marine s earlier work [43] Thus the contribution of the nodular tissue to total thyroid function was small and not at all in relation to its size The hormone producing capacity of nodules found associated with exophthalmic goiter or toxic nodular goiter was similarly much less than that of the surrounding hyperplastic tissue in fact these nodules were functionally autonomous acting like the nodules found in non toxic nodular goiter

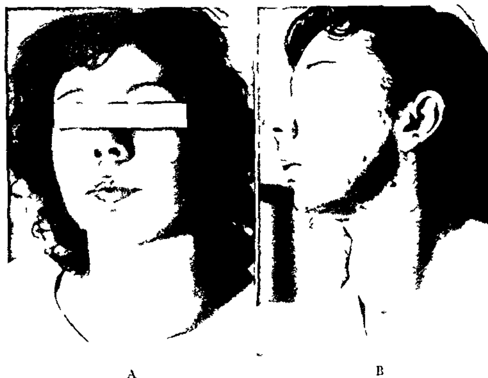
The avidity of all these nodules for radio iodine was less than that of the surrounding thyroid tissue This contrasts sharply with the behavior of the rarely encountered hyperfunctioning adenoma of the thyroid which has been shown by Cope and his associates [44] to be more avid for radio iodine than the perinodular tissue Such hyperfunctioning nodules undoubtedly produce more hormone than the surrounding thyroid tissue as evidenced by atrophy of this tissue and cure of the associated thyrotoxicosis by enucleation of the nodule

Symptoms and Signs

The symptoms produced by non toxic nodular goiter depend upon the size and location of the nodule or nodules Location is more important than size for a small nodule that is partly substernal may produce marked pressure symptoms through obstruction of the narrow thoracic inlet whereas a large nodule completely suprasternal may disfigure without producing symptoms The arrangement of the bones muscles and fascia of the neck hinder upward backward and lateral extension of the cervical goiter but do favor anterior or downward growth Gravity and the respiratory movements combined with the lack of containing muscles or fascial planes further aid in the downward propagation of nodular goiter It is for this reason that many cervical goiters have subclavicular substernal or intrathoracic components conversely the substernal or intrathoracic goiter is almost always found to be partially suprasternal If pressure symptoms occur they are similar to those produced by large colloid goiters namely cough dyspnoea hoarseness and dysphagia

The physical findings depend largely upon the stage of the disease. Early in the course of the process small nodules may be imbedded so deeply in a diffuse colloid goiter that they are neither visible nor palpable. With progressive involution of the surrounding colloid the nodules become more apparent. In addition there is a tendency for the nodule to enlarge with age.

Nodular goiters are easily recognized by inspection and palpation.



A B

Fig 4. L. F. (B.I.H. No 53561) a 35 year old woman native of Maine with large cystic goiter of 10 years duration and with symptoms and signs of hypothyroidism for 2 years preceding thyroidectomy. Thyroidectomy 7/14/40. Pathologist reported involution nodules with cystic degeneration.

Asymmetrical enlargement may be seen and felt. Single or multiple nodules may be present. The consistency, circumscription and mobility of the nodule should be carefully noted. Calcareous deposits, carcinoma or thyroiditis produce extremely hard masses. Cystic changes may produce fluctuant translucent swellings. Murmurs may be audible in this *latter instance but ordinarily murmurs and thrills will be absent in non*toxic nodular goiters. The essential information sought in the examina-

tion is the demonstration of a discrete and circumscribed mass or masses distinct from surrounding thyroid parenchyma the degree of tracheal deviation and compression and the attachment of the mass to surrounding tissues Roentgenography is necessary for the demonstration of tracheal compression and of substernal extension Laryngoscopy will reveal impairment of vocal cord motion due to injury to the recurrent laryngeal nerve (Figs 4 6)

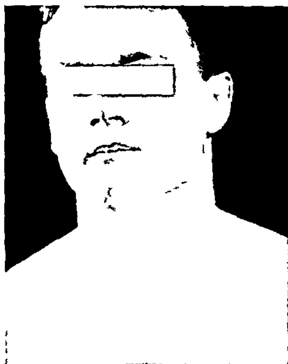


Fig 43 A D O B (BIH No 5 36) Multinodular colloid goiter in a euthyroid boy aged 17 native of Boston with a history of goiter since age of 8 or 9 and recent increase in size with mild pressure symptoms Thyroidectomy on 3 31/49 showed multiple colloid nodules



Fig 43 B Profile view



Fig 44 B D (BIH No 96? 0) a 63 year-old euthyroid woman native of Massachusetts with multinodular goiter of 42 years duration increasing in size and producing pressure symptoms during the 2 years preceding thyroidectomy Thyroidectomy on 10/ 8/47 showed multiple colloid masses in various stages of biological change No malignancy was found

Fig 45 A J G (B I H 88 A) Calcified thyroid cyst in a man aged 5 with cough dyspnoea and dysphagia Postero anterior view showing large cyst with calcified wall displacing and compressing the trachea from the right



Fig 45 B J G (B I H 882A) Oblique view



Fig 46 A B (BIH p 48-450I) Nodular non toxic goiter in man aged 59 with cough and dysphagia Postero anterior view of a large ovoid calcified mass to the left and anteriorly to the trachea and esophagus Its lower pole reaches below the jugular notch The esophagus is filled with barium

Clinical Course

The clinical development of nodular goiter may proceed along several courses. The nodule may remain the same for long periods of time, it may grow and press on neighboring structures, it may degenerate or be the site of hemorrhage, it may be neoplastic, either benign or malignant, it may rarely hyperfunction within itself or, more commonly, be associated with perinodular hyperfunction, and, very rarely, it may involute and disappear altogether.

Thyrotoxicosis may develop in patients who have had asymptomatic nodular goiter for many years. In most instances the nodule is an incidental pathological finding in a diffusely hyperplastic gland. In a small number of cases the nodule itself is both hyperplastic and hypersecretory and is surrounded by an involuted or atrophic thyroid parenchyma.[43] Eventually a considerable number of patients with nodular goiters will develop thyrotoxicosis. The incidence of this development varies considerably. Means[4] has reported an incidence of 13 per cent in a series of patients with nodular goiter seen at the Massachusetts General Hosiptal. At the Mayo Clinic, Plummer[46, 47] has found that 60 per cent of patients with nodular goiter over the age of 60 had associated thyrotoxicosis, whereas only 5 per cent of those under the age of 30 had a similar association. He also noted that the average duration of a nodule before the appearance of hyperthyroidism was about 17½ years. At the Beth Israel Hospital we have found co-existent hyperthyroidism in 19.5 per cent of 200 patients with nodular goiter.

The etiologic relationship between pre-existing benign nodules and the development of thyroid carcinoma is difficult to establish in spite of the incidence of malignancy in surgically excised thyroid nodules. This subject has been reviewed by us on the basis of the pathological findings in 200 cases of nodular goiter treated by thyroidectomy.[49] In our series 14.4 per cent of solitary nodules were malignant neoplasms and 10.4 per cent of patients with multinodular goiter had malignant thyroid neoplasms (Table VI). A more extensive discussion of the relation of nodular goiter to thyroid cancer will be found in the section on thyroid neoplasms (Part X).

Diagnosis

The finding of one or more discrete nodules within the substance of the thyroid gland is the only requisite for the diagnosis of nodular

TABLE XI

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PATHOLOGY AND INCIDENCE OF CANCER IN THYROIDS WITH SINGLE AND MULTIPLE NODULES

Pathologic diagnosis	*Number of cases with*	
	Single nodule	*Multiple nodules*
Embryonal adenoma with blood vessel invasion	4	1
Fetal adenoma with blood vessel invasion	1	
Papillary carcinoma	7	8
Epidermoid carcinoma	1	
Scirrhous carcinoma	1	
Giant cell carcinoma	1	
Diffuse small-cell carcinoma		1
Total	15	9
Total cases	[illegible]	
The incidence of cancer of the thyroid in 200 cases of nodular goiter		12 5
The incidence of cancer in single nodules		14 4
The incidence of cancer in thyroid with multiple nodules		10 4

The incidence is calculated from the number of patients and not from the number of nodules

goiter The functional state of the thyroid is determined by the procedures outlined in the preceding Part In addition it is possible to discover the functional state of the nodule itself by means of directional counting with a scintillation counter or a properly designed Geiger Muller counter following a tracer dose of radioactive iodine [49] The thyroid nodule whether colloid or carcinomatous will have a measurably decreased uptake as compared with surrounding thyroid tissue except in the occasional instance of a hyperfunctioning nodule in which case the nodule will show a high uptake and the rest of the thyroid gland a depressed uptake Patients with non toxic nodular goiter will have no signs or symptoms of thyrotoxicosis but occasionally may show evidence of decreased thyroid function Substernal extension should be visualized by roentgenography Pressure from the nodule on neighboring structures may be recognized by noting tracheal deviation and compression as well

as by the symptoms of cough dyspnoea, hoarseness (from paralysis of the recurrent laryngeal nerve), and rarely dysphagia

The development or presence of malignancy cannot be determined clinically in most instances While a history of recent growth may be misleading because it may be due to hemorrhage within the nodule, in general rapid growth is suggestive of malignant neoplasm Unusual firmness attachment to neighboring structures fixation of overlying skin, distention of neck veins and enlargement of regional lymphodes all point to malignancy Chronic thyroiditis whether lymphadenoid goiter or Riedel s Struma may simulate thyroid cancer, biopsy alone being determinative

Treatment

It is clear from the clinical course and pathology of non-toxic nodular goiter that benign growth with pressure upon neighboring structures the occurrence of malignancy and the development of thyrotoxicosis are hazards commonly associated with this type of thyroid disease Thyroidectomy is clearly indicated for the relief of pressure symptoms Associated thyrotoxicosis is no longer in itself an indication for operation since other measures are available for the control of hyperthyroidism The need for thyroidectomy in toxic nodular goiter arises from the clinical uncertainty regarding the pathology of the nodule and the argument for thyroidectomy is in no way affected by the functional state of the thyroid

Single or multiple nodules of the thyroid unassociated with either pressure symptoms or hyperthyroidism may be subdivided further from the point of view of therapy (1) those that are probably malignant as determined by a history of rapid growth or unusual firmness and ( ) those that *appear clinically benign In the first group* thyroidectomy is definitely indicated In the second group thyroidectomy is clearly indicated for the solitary nodules and less certainly for the multiple nodules

While our own experience has shown the incidence of carcinoma in surgically excised nodules to be about 1[illegible].5 per cent (Table vi), we cannot agree entirely with the point of view advanced by Hinton[51] who suggests that thyroid nodules should be treated like nodules in the breast —namely by surgical investigation of all cases The clinical course of breast cancer is radically different from that of the commoner types of thyroid malignancy in that the former is more rapidly invasive and more frequently metastatic than the latter Thyroid cancers especially the

papillary adenocarcinoma may remain locally malignant for many years. Their slowness of growth is such that observation over long periods of time may be necessary to grasp their essential kinship to other forms of cancer. In these circumstances, while thyroidectomy is generally advisable, it may be voided altogether in the aged and in those with short life expectancy because of concurrent disease. It may be cautiously deferred in those with multinodular goiter who will agree to frequent clinical observation. In such patients, desiccated thyroid (U.S.P.) in doses of 0.120 to 0.180 gm. (gr. 2 to gr. 3) daily may be given for periods of several months to achieve the occasional disappearance of an incompletely encapsulated colloid nodule. Thyroid medication also may prevent the development of further colloid nodules and will cause regression of perinodular thyroid enlargement.

An adequate operation for benign nodular goiter should consist of either unilateral or bilateral subtotal or total thyroidectomy, depending upon the number and extent of the nodules. Simple enucleation of the nodule or nodules is followed by a relatively high incidence of recurrent nodules. Means[45], for instance, has found 1 times the rate of recurrence after simple enucleation as compared to that after subtotal thyroidectomy. Furthermore, it is certainly inconsistent to operate in a minimal way for possible carcinoma. With single nodules the contralateral lobe should be exposed and inspected.

All nodules after removal should be immediately sectioned by the surgeon or the pathologist, and frozen section examinations should also be made in those instances in which there is capsular invasion or attachment to neighboring structures. The therapy of malignant nodules of the thyroid will be discussed in the section on malignant neoplasms of the thyroid (Part X).

III. INTRATHORACIC GOITER

Intrathoracic goiter is a form of nodular goiter which has extended downward into the thorax. It is a special type by virtue of its anatomical location but has the usual range of pathological changes found in cervical or extrathoracic nodular goiter. The majority of these goiters are partially intrathoracic, lying for the most part below the clavicle or substernally, with a cervical component of varying degree that can be palpated. Completely intrathoracic goiter, lying wholly within the thorax, is rarely seen.

Intrathoracic goiter arises as an extension downward of a nodule in the lower pole of either thyroid lobe. The anatomical structures of the neck favor descent of such nodules into the superior mediastinum especially after the upper thoracic inlet has been passed. The clinical picture produced is therefore the result of pressure from the mass upon surrounding structures, especially the trachea, the great veins, the esophagus and the recurrent laryngeal nerve. Occasionally there may be associated thyrotoxicosis and malignant degeneration as with cervical nodular goiter.

Dyspnoea and cough are the chief presenting symptoms. The dyspnoea may be severe and associated with noisy or stridorous breathing. It is due to compression, kinking, deviation and torsion of the trachea by the substernal mass or masses. Wheezing may be present simulating bronchial asthma. Nocturnal dyspnoea is also characteristic because of increased angulation of the trachea in the varying positions assumed during sleep. Cough ensues because of associated bronchitis and tracheitis. Dysphagia is not uncommon owing to compression and deviation of the esophagus, but severe dysphagia is uncommon. Paralysis of the recurrent laryngeal nerve with attendant hoarseness is rare according to Lahey, but it occurred in 13 per cent of the cases in Higgins' series.[1]

Venous engorgement of the chest and neck usually occurs with large intrathoracic goiters, especially those appearing on the right side because of pressure on the great veins, particularly the superior vena cava. The vessels of the neck may be displaced laterally and forward. Edema of the head and neck may be present.

The diagnosis may be suggested by the symptoms outlined above and by the finding on direct examination of the upper portion of the intrathoracic mass. This can be detected in nearly all cases if palpation is carefully done during deglutition or at the end of deep expiration. This is an important feature differentiating these masses from other mediastinal tumors. Roentgenography is of course invaluable for the demonstration of an intrathoracic growth but will not always establish a clear diagnosis of its nature.

The treatment of intrathoracic goiter is exclusively surgical. Removal of large intrathoracic goiters is hazardous when compared with the relative harmlessness of thyroidectomy for cervical non toxic nodular goiter. The risks of operation are greater—first by virtue of the location, secondly because hemorrhage and resultant surgical shock are commoner and more difficult to control, and finally because the patients are usually older with more associated cardiovascular disease. For these reasons it is advisable to remove all low lying thyroid nodules which tend

to descend subclavicularly during the course of observation or which are partially subclavicular when first seen (Figs 47 48 49)

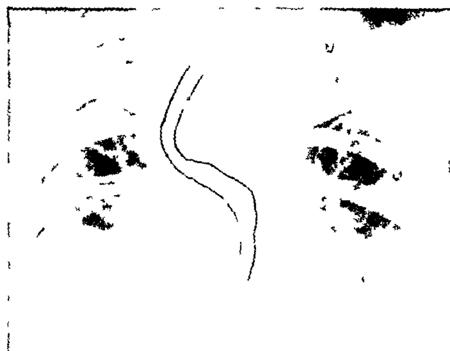


Fig 47 A I B (BIH A1333) Non toxic nodular goiter in a woman aged 60 with cough and dysphagia Postero anterior view showing marked displacement to the right and anteriorly of the esophagus (outlined) and trachea by a large mass located mainly to the left and posteriorly and extending two cms below the sterno-clavicular joint





Fig 48 P H (B I H A 567) Substernal goiter in a man aged 61 with cough wheezing dyspnoea Anteroposterior view showing a large mass compressing and displacing the trachea and esophagus to the right The esophagus is filled with barium The mass extends down beneath the sternum to the level of the aortic arch



Fig 47 B I B (BIH A13330) Left oblique view with esophagus filled with barium

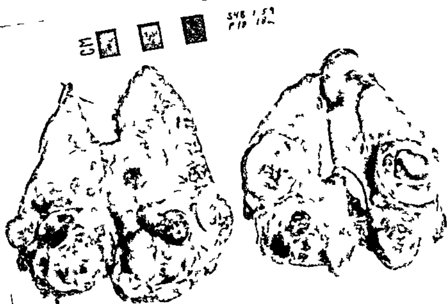


Fig 49 B Appearance of nodules and cysts in cross section of the thyroid Histologically the nodules were hyperinvolution bodies in various stages of biological change many showing hemorrhage and cyst formation None showed malignancy



Fig 49 A Benign multinodular substernal goiter producing severe pressure symptoms successfully removed on 4/ 6/48 from L C (B I H No 098,4) a 6 year old female with acromegaly

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PART VII

TOXIC GOITER

I. TOXIC DIFFUSE GOITER

II. TOXIC NODULAR GOITER

Introduction

Definition. A characteristic clinical syndrome of unknown etiology associated with diffuse symmetrical enlargement of a previously normal thyroid gland, a variety of eye changes, elevated basal metabolism, and increased circulating thyroid hormone. The clinical manifestations vary greatly from the florid cases exhibiting all the classical signs of goiter, exophthalmos, tachycardia, and tremor to those with apathy, weakness, somnolence, and muscular wasting without exophthalmos or significant enlargement of the thyroid.

Synonyms. These are in two groups—eponymic and descriptive. Of the former the most widely and justifiably used are the following: Parry's disease, Graves' disease, and Basedow's disease or Basedowism. The descriptive terms that have been applied include the following: exophthalmic goiter, hyperthyroidism, and thyrotoxicosis.

Historical. Although Flajani[1] is credited with one of the earliest descriptions, his statement cannot be considered as an accurate account of the disease. Caleb Hillier Parry, however, deserves credit for the first recognizable description of this syndrome; he apparently considered it a form of heart disease. His writing on the subject, published by his son in 1825, three years posthumously, begins as follows: "There is one malady which I have in five years seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland." This is followed by a report of eight cases showing goiter with tachycardia, exophthalmos, and edema; of seven cases of thyroid enlargement with tachycardia or palpitation; and of five cases of thyroid enlargement without heart symptoms.

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this disease This point of view has been upheld by the studies of von Mueller[16] and Aschoff[17] Crotti[18] in fact claimed an even higher incidence of toxic goiter in regions of endemic goiter Sallstrom[19] however *reporting from Sweden found no correlation between the incidence of toxic and endemic goiter*

In the United States McClendon and Hathaway[20] utilizing data from the U S Army draft records concluded that the geographical incidence of simple and exophthalmic goiter was so similar both occurring in the iodine poor areas of the country that they ascribed both diseases to simple iodine want Their sampling was derived from a male population limited in age and cannot be considered accurate *In addition the diagnosis was frequently in error since careful distinction was not made* between neurocirculatory asthenia common in army recruits and thyrotoxicosis Read[1] in a comprehensive and well considered study of geographical distribution based his findings on questionnaires sent to large representative hospitals throughout the United States The incidence of thyrotoxicosis in over 400 hospitals in a ten year period was then calculated *The average incidence of exophthalmic goiter in 14 million hospital* admissions was found to be 0 57 per cent with a range from 0 6 per cent in the southern states to 1 65 per cent in the Pacific northwest Toxic diffuse goiter occurred more uniformly throughout the country than did simple or iodine deficiency goiter although there was a somewhat higher incidence of toxic goiter in the areas of endemic goiter Large urban communities whether in goitrous or non goitrous regions had a particularly high incidence a finding in accord with that of Sallstrom[11] in Sweden

The disease is more common in women the exact ratio between the sexes varying somewhat in goitrous and non goitrous areas usually being about 5 1 in the latter and 5 3 in the former regions No race appears to be immune as typical cases have been reported from every part of the world

The age of onset is most commonly in the third decade regardless of geographical location but it may occur from early infancy to advanced old age Classical toxic diffuse goiter has been described in an infant at birth the mother having had exophthalmic goiter during the pregnancy[22] and Elliot[3] *has encountered it during the first year of life* Gardiner Hill[4] studied age incidence statistically and found that women show three peaks of high incidence (1) single girls between puberty and twenty four (2) married women from twenty five to forty two and (3) married women at or about the climacteric

In 1835, Graves[3] of Dublin in the twelfth of a series of lectures incidentally described the syndrome which bears his name The subjects covered in this lecture were 'Persesquinitrate of Iron in Chronic Diarrhea—Blueness of Fingers and Toes in Fever—Some Account of the Yellow Fever which Prevailed in Dublin in 1827—Newly Observed Affection of the Thyroid Gland in Females Its connexion with palpitation with fits of hysteria—Erysipelas—Remarks on the Formation of Acidity of the Stomach in Indigestion—Psoriasis—Treatment by Arsenic Graves described three cases in females All had exophthalmos thyroid enlargement tachycardia, and palpitation Loss of weight, emaciation nervousness diarrhea night sweats and edema were also noted

Basedow[4] in 1840 also published an early and classical description of the disease emphasizing particularly the exophthalmos He ascribed the disease to a blood dyscrasia which by reason of some as yet unknown scrofulous taint takes the form of glandular growths and tissue hypertrophy ' Probably the first autopsy in a patient with exophthalmic goiter was performed by Basedow He also appears to have used spring water rich in iodine for the successful treatment of a severe case of thyrotoxicosis and to have mentioned iodides as valuable in the treatment of the disease

Trousseau[5] Charcot,[6] and Marie[7] were particularly impressed by the nervous manifestations of thyrotoxicosis, indeed they considered the disease to have a nervous origin and the thyroid enlargement to be a secondary incident Mobius,[8] in 1886 first suggested that a pathological thyroid gland was the primary cause of the malady Subsequently Greenfield[9] Lubarsch,[10] Stewart and Gibson[11] Horsley[1] and Edmunds[13] described hyperplasia of the thyroid as an invariable accompaniment of thyrotoxicosis

Distribution and Incidence

The geographical distribution of toxic diffuse goiter is not precisely known It is not a reportable disease and does not have such a high or inevitable mortality that autopsy statistics will yield significant figures on distribution Estimates of its frequency therefore, have been derived from clinical impressions garnered from Army draft records dealing with males only or deduced with some accuracy from the statistics of large urban hospitals McCarrison[14] found exophthalmic goiter to be rare in areas of goiter endemicity Kocher[15] however reported that in Switzerland goitrous and non-goitrous regions had equal incidence of

Marlham[30] first noted hyperplasia of the thymus in the disease and subsequently it has been demonstrated that thymic hyperplasia or regeneration occurs in three fourths of patients under the age of 30. This lymphoid hyperplasia is reflected in the lymphocytosis of the blood which is so common in exophthalmic goiter and also reveals itself in lymphocytic infiltration in the thyroid gland itself. Warthin[2] felt that there was a typical Graves constitution which had to exist before the disease could occur and that this constitution was typically characterized by generalized lymphoid hyperplasia. Marine[4] has accepted the general idea of a predisposing constitutional type but considers that it may be acquired through various mechanisms, especially those wherein sublethal adrenal injury has occurred.

Moschcowitz[31] has likewise emphasized the constitutional background as an important factor in the cause of exophthalmic goiter. By constitution he means the mental and emotional make up of the patient, however, rather than any specific physical type. The Graves personality, according to this concept, is that of the sensitive emotional type and it is present before, during and after the disease. The specific personality type is frequently familial and hereditary. Lorand and Moschcowitz[3] in a psychoanalytic study of 50 patients with Graves disease found their sensitivity of temperament explicable on the basis of excessive protection by the mother in early childhood. This led to infantile reactions in adult life and an inability to cope with its usual hardships.

Current trends in psychosomatic medicine do not stress specific emotional types or hereditary predispositions but do make much of emotional conflicts existing at the time of onset of the disease.[33] Conrad[34] found disturbances in the mother child relationship but of a type opposite to that found by Lorand and Moschcowitz[3] for in her series a large number of patients had lost their mothers at an early age, others had been unduly imposed with responsible burdens by the mothers. In her series psychic trauma was demonstrated in 94 per cent of the cases. In reference to this entire subject Joll[35] the English surgeon sagely remarks that it is not possible to estimate the real significance of these factors in the causation of the disease until we know whether a history of worries and emotional strains is more common among those suffering from exophthalmic goiter than among the general population.

Shock

In some instances a severe shock or fright may be followed by thyro

Etiological Factors

Though the cause of toxic diffuse goiter is unknown, many facts relevant to its pathogenesis are available. All theories of causation must be adequate to explain the two striking features of the disease, namely the exophthalmos and the hyperfunctioning goiter.

Heredity

The hereditary background of exophthalmic goiter has been discussed extensively because of the frequency of multiple cases in the same family. Thorough investigations of this aspect of the disease have been published by Bartels[6] and Martin.[7] These studies are of particular importance because they are based on careful analyses of relatively large numbers of cases personally investigated by the authors. Bartels[78] reported 197 cases of toxic goiter, both diffuse and nodular. In 69 cases of toxic diffuse goiter a family history of toxic goiter was found in 42 per cent. He concluded that there was a recessive Mendelian characteristic responsible for the inheritance of exophthalmic goiter, and that this characteristic was partially sex-linked, since 70 to 80 per cent of the cases occurred in women.

Martin[7] examined 90 adults with exophthalmic goiter and constructed detailed family trees in 35 cases. He also simultaneously studied a somewhat larger group of patients with toxic and non-toxic nodular goiter. He found that female relatives of patients with exophthalmic goiter were affected 6 times more frequently than male relatives, and that sisters were most commonly involved. While male relatives were rarely affected, brothers manifested the disease most commonly. Finally, patients with exophthalmic goiter had more relatives with this disease than did patients with nodular goiter by a ratio of 8.5:1.

Martin's statistics, when subjected to analysis by Prof. R. A. Fisher, the British geneticist, indicated a qualitative tendency of recessive inheritance rather than environmental influences or inheritance of a dominant type. There was no evidence favoring heredity in nodular goiter.

Constitution

A characteristic physical or mental constitution predisposing to the development of Graves' disease has been stressed by some authors.

in iodine deficiency or with thiouracil administration and hyposecretion of the hormone In addition the administration of iodine is quickly followed by colloid storage in the thyrotoxic gland

The hypersecretory activity of the thyroid gland in Graves disease cannot be adequately explained on any known basis of internal abnormality

Role of the Anterior Pituitary

The interrelations of the thyroid and the anterior pituitary have been discussed in Part II The thyroid is largely dependent on thyrotrophin from the anterior pituitary for maintenance of its structural and secretory capacity Thyrotrophin is probably derived from the basophilic cells of the adenohypophysis It produces an increased height of the follicle cells hypertrophy and hyperplasia of the epithelium colloid resorption increased vascularity and enlargement of the gland These are the very changes which are so characteristic of the goiter of Graves disease

Thyrotrophin also causes a decrease in the iodine and hormonal content of the thyroid gland simultaneously with an increase in the hormonal iodine of the blood—Kocher s thyroid diarrhea In addition the pituitary hormone augments the rate of conversion of inorganic iodine into thyroxine The release of thyroid hormone into the blood is controlled by thyrotrophin to such an extent that with adequate stimulation a hormone free thyroid gland can be produced Moreover either thyrotrophin itself or closely associated substances derived from the anterior pituitary have regularly produced exophthalmos in many species of experimental animals The orbital tissue changes in patients with thyrotoxicosis have been found indistinguishable from those produced by injections of anterior pituitary extract

Is thyrotoxicosis therefore a disease initiated and maintained by overactivity of the anterior pituitary This is an attractive hypothesis with an extensive experimental background There are not yet available enough facts to support this idea however In patients with toxic goiter pathological changes in the anterior pituitary have not been demonstrated No substantial proof is available of increased thyrotrophin secretion or circulation in exophthalmic goiter much of the difficulty is due to the inadequacies of extant methods of hormone assay Furthermore typical hyperthyroidism is rarely associated with clear cut examples of pituitary overactivity as occur in acromegaly or pituitary basophilism Again if

toxicosis—Schreckbasedow—i e, Basedow's disease of fright origin Such cases undoubtedly exist but in many instances in our experience it is difficult to determine whether the acute fright has precipitated Graves disease or has merely aggravated an existent mild case Traumatic shock cannot be a very significant factor among men at any rate since neither World War I nor II resulted in any great increases in the disease among soldiers or civilians

Neurogenic Factors

Several authors, particularly Eppinger and Hess,[36] von Noorden Jr[37] and Kessel, Hyman and Lieb[38] have ascribed toxic goiter to an imbalance of the autonomic nervous system in the direction of excessive sympathetic tone In terms of modern physiology this idea might be expressed as increased adrenergic activity or decreased cholinergic action No satisfactory proof has been adduced to support this point of view Indeed it is well established that thyrotrophin will act on the thyroid quite independently of nervous tissue (see Part II) While thyrotoxic patients and animals may have an increased sensitivity to epinephrin this is far from universal or constant

Role of the Thyroid Itself

Moebius in 1886[39] and later Plummer[40] have theorized that thyrotoxicosis may be due to the secretion of an altered hormone Because of the characteristic beneficial effect of iodides in thyrotoxicosis and the greater potency of thyroglobulin derived from thyrotoxic glands Plummer suggested that a less iodized hormone was elaborated and that this hormone was responsible for the symptoms of hyperthyroidism This hypothesis has been refuted quite convincingly by the work of the bio chemists[41, 42, 43] who have demonstrated the lessened calorigenic activity of thyroxine derivatives containing less iodine Since Kocher[44] introduced the concept of a thyroid diarrhea as occurring in toxic goiter, and since in fact there occur high levels of circulating hormone associated with low values of gland hormone one might postulate an inadequate storage capacity of the thyroid in Graves disease associated with the continued secretion of normal hormone There can however be no true loss of storage capacity (i e ability to form colloid) in this disease since the hyperplasia of the gland is not distinguishable from that seen

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an overactive pituitary is the *vis a tergo* in Graves' disease, how can we explain the fact that all successful methods for curing clinical thyrotoxicosis depend on either destruction or restriction of the thyroid parenchyma, as with subtotal thyroidectomy or radioactive iodine, or on mechanisms for interfering with hormone synthesis, as with thiourea derivatives, or on interference with hormone delivery through increasing colloid storage as with inorganic iodine. Iodine is the only therapeutic agent that also exerts an inhibiting effect on thyrotrophin and it is the least certain of available therapeutic methods for accomplishing complete remission.

Role of the Adrenals

Marine [30] has stressed the fact that adrenalectomy or sublethal injury to the adrenal cortex results in increased metabolism in animals with intact thyroids. This has been confirmed by others (see Part II). Increased metabolism, however, is only part of the picture of thyrotoxicosis and in the instances where it follows adrenal injury, may be due to effects on the adrenal medulla. Epinephrine is highly calorigenic. It will produce thyroid hyperplasia through increased thyrotrophin circulation. We have seen two instances of thyrotoxicosis in patients with Addison's disease but such cases are certainly exceptional. Perera and Porter [5] were able to find only two cases of proved co-existence of Addison's disease and toxic goiter.

Miscellaneous Factors

Various miscellaneous factors have received some consideration as causative agents in toxic goiter. Infectious agents and infections have frequently been cited as the cause of the disease [46, 47] particularly in the earlier literature when the theory of focal infection was in vogue. King [4] for example, reported a high incidence of tonsillar infection in exophthalmic goiter and believed that tonsillectomy might prevent recurrences.*

The ingestion of desiccated thyroid as a factor in the subsequent precipitation of thyrotoxicosis in some cases has been emphasized by the

* Many epidemics of thyrotoxicosis have been reported. The Danish epidemic of 1941-5 as described by Meulengracht (Meulengracht, E.: Epidemiologic aspects of thyrotoxicosis. Arch. Int. Med., 1949, LXXXIII, 119) represents the most carefully documented and analyzed epidemic on record. Meulengracht believes that it may have been infectious in origin and asks for an open mind on the possibility of a specific infective agent of unknown nature as a cause of thyrotoxicosis.

Scandinavian authors Bruun[48] and Lous[49] The former found that 3 per cent of 485 cases of thyrotoxicosis had been under treatment with thyroid substance for obesity or other non thyrogenous medical ailments shortly preceding the onset of thyrotoxicosis Lous[4] reported nine patients who developed typical Graves disease within six months after they had begun to take thyroid extract In these cases the basal metabolism was known to be normal prior to the initiation of thyroid medication Thyroidectomy was performed in most of these patients and resulted in the finding of hyperplastic glands

Hertz and Means have stressed weight loss as a possible factor in some cases of thyrotoxicosis on the basis of 20 cases of hyperthyroidism that developed following significant weight loss from various non thyrogenous causes including rigid dieting with or without thyroid medication

It is difficult to evaluate the effects of preceding thyroid ingestion or pronounced weight loss as factors in the causation of toxic goiter in view of the commonness of the disease and the likelihood of coincidence

The etiology of toxic goiter is therefore still unknown but the factors most securely established in an important relation to its cause are (1) heredity (2) a predisposing psychosomatic constitution and (3) significant mediation through hormones of the anterior pituitary

Pathology

Thyroid Gland

The degree of enlargement of the thyroid in toxic diffuse goiter varies considerably but in general is slight to moderate never reaching the huge size so often encountered in the non toxic diffuse or nodular goiters Thyroid enlargement may be absent clinically this will be readily understood as the microscopic pathology is reviewed and the distinction between hyperplasia and hypertrophy clarified Hyperthyroidism associated with a completely intrathoracic goiter exhibiting only diffuse hyperplasia without nodule formation is extremely rare but low lying subclavicular or partially substernal glands are not uncommon—these are readily discovered by examination during swallowing

The gross appearance of the toxic gland will depend on previous treatment the occurrence of remissions and occasionally on the acuteness and severity of the disease In the completely untreated case the gland is diffusely enlarged with a finely lobulated almost smooth surface

The consistency is firmer than that of the normal gland, resembling the pancreas On section, the appearance is usually opaque and beefy, uniform in color, contrasting with the translucence of colloid goiter Ordinarily the stroma is inconspicuous but in long standing cases prominent connective-tissue septa develop, giving a distinctly lobular appearance Nodules of varying size may be seen, representing the hyperinvolution bodies of Rienhoff The increased vascularity of the hyperplastic gland is best seen in the operative field rather than on the pathologist s block after draining and collapse of the vessels have occurred Previous administration of iodine alters the gross picture considerably resulting in involution toward the colloid type of gland This is rarely complete so that while the iodinized gland is generally translucent it may contain numerous opaque areas representing non involuted islands of hyperplasia

The microscopic picture of the thyrotoxic gland is not uniform but is ordinarily characterized by changes in the acinar epithelium the colloid the blood vessels and by the frequent appearance of lymphocytic infiltration The exact histology is determined by the balance between hyperplasia and involution, this in turn is dependent on the stage of the disease and previous therapy

Hyperplasia of the thyroid has a unitary pathology but diversity of cause In hyperplasia proliferation of the epithelial cells occurs The cuboidal cell of the normal or resting gland is replaced by tall columnar cells Mitoses, indicating cell division are common The cytoplasm of the cell stains feebly and contains many granules and globules Mitochondria are greatly increased and the Golgi apparatus exhibits changes characteristic of increased cell activity [50] The follicle space enlarges to accommodate the proliferating epithelial cells, which project or papillate into the acinus so that it may become almost solidly filled The colloid representing the stored hormone inevitably alters in appearance staining poorly with eosin becoming vacuolated in the portions contiguous to the acinar cells and frequently disappearing altogether Vascularity is increased and lymphocytic nests may occur These latter changes are more specific in Graves disease and do not necessarily occur as part of the general hyperplastic process

In untreated thyrotoxicosis the picture of hyperplasia presents itself in two general forms Usually there is increased acinar size without increase in the number of acini There is marked papillary infolding of the epithelium which may fill or partially fill the lumen The increased acinar size is not apparent until the involution process causes regression of the papillary buds, thus exposing the increased size of the individual

acinus Less commonly hyperplasia may manifest itself by an increased number of acini of small size lined by very high columnar epithelial cells without papillation into the acinar lumen The changes in the colloid are the same in both types of hyperplasia—it is scanty poorly staining vacuolated and often absent

The stroma of the hyperplastic thyroid gland of Graves disease shows two characteristic changes namely increased vascularity and lymphoid infiltration Warthin [79] considered this latter finding as an indication of the Graves constitution—an obligatory requisite for the development of thyrotoxicosis The degree of lymphocytic infiltration may vary from small collections to definite follicle formation Boyd [5] has found that the use of iodine with establishment of involution increases the incidence of lymphoidosis A similar finding has been reported after the use of thiouracil [53]

The picture of hyperplasia in the thyrotoxic gland is never uniform even in the uniodinized patient owing to the tendency to involution which over a long period may gain ascendancy over the hyperplastic process with remission of the disease The process of involution may therefore result from exhaustion of the hyperplastic activity or it may be readily induced by administration of iodine Histologically involution is characterized by enlarged and markedly distended acini lined with low cuboidal or flattened epithelium and containing within their lumen increased amounts of deeply staining colloid and occasional remnants of papillary projections The fibrous tissue of the stroma is increased while the vascularity is diminished

Rienhoff [54] studied the development of involution in the thyroid glands of patients with Graves disease before and after treatment with Lugol s solution Before iodinization the thyroid showed typical hyperplasia After iodine had been administered partial complete or excessive involution became manifest Grossly the average involuted gland had lost its smooth surface because of the appearance of nodules of various sizes and cystic areas containing fluid These nodular and cystic areas result from an intensive involution termed hyperinvolution by Rienhoff In the same thyroid gland all degrees of involution co existed Microscopically hyperinvolution manifests itself by abnormally distended acini often of enormous size lined by cells so attenuated that eventually coalescence of several acini into large cavities containing dense colloid occurs This hyperinvolutionary process takes place discretely within the lobule so that large colloid areas develop surrounded by connective tissue Compression and obliteration of surrounding acini occur and the colloid

area surrounded by its capsule of fibrous tissue forms a typical colloid nodule

This sequence of hyperplasia, involution and nodule formation may be repeated many times thus leading to single or multiple nodules The colloid nodule that has evolved from this sequence cannot, therefore be regarded as a true tumor but only as the natural result of hyperplasia regardless of cause Most colloid nodules do not represent a terminal phase of the hyperplasia of thyrotoxicosis but rather of that resulting from the causes of non toxic diffuse goiter already discussed in Part vi Nevertheless it is not rare to find patients with colloid nodules of varying size who present the residual stigmata of a previous pre existent episode of exophthalmic goiter

Pathology of Extrathyroidal Tissues

The treatment of toxic goiter by thyroidectomy has afforded abundant material for extensive study of the pathological changes in the thyroid gland in every stage of the disease and after the use of many therapeutic agents such as iodine thiourea derivatives irradiation and radioactive iodine Knowledge concerning extrathyroidal tissue however has been necessarily derived chiefly from autopsy material This material is meager and in many instances has been obtained from patients dying in acute thyroid crisis This has added terminal factors of metabolic disintegration that may have little to do with the intrinsic pathology of toxic goiter

The available knowledge is concerned largely with pathological changes in the orbital tissues lymphoid tissues including the thymus the liver the muscles the bones and the heart Information is slight with regard to the other endocrine organs such as the pituitary the adrenals and the gonads

Orbital Tissues

The alterations in the tissues of the orbit produced in animals by thyrotrophin have already been described and have been compared to some extent with the changes found in thyrotoxic patients (see Part ii) The changes in the eye muscles are part of the generalized myopathy which may occur in thyrotoxicosis as first found by Askanazy in 1898[65] He described interstitial fibrosis with lymphorrhages in voluntary stri

ated muscles and in the extra ocular muscles particularly in severe exophthalmos Mulvany [6] found degenerative changes in the extra ocular muscles indicated by wasting and irregularity of the muscle fibres disintegration of the nerve supply loss of striation granulation of the sarcoplasm and reduplication of the sarcolemmal nuclei The extra ocular muscles may be entirely normal however in thyrotoxicosis when it is not associated with severe or malignant exophthalmos All are agreed [7, 8, 9] that in this latter instance the muscle changes are well marked consisting of chronic hypertrophic myositis with interstitial fibrosis edema and lymphocytic infiltration with frequent germinal centers The muscle hypertrophy is enormous Basedow [4] and much later Smelser [62] have shown that there is diffuse hyperplasia of all the orbital contents particularly of the fat There is also edema fluid present with wandering cells in the fat connective tissue and muscles The edema fluid stains with eosin and anilin blue and is found infiltrating between the connective tissue the muscle fibers and the fat cells Rundle and Pochin [61] have emphasized the increased fat content of the orbital tissues as an important cause of exophthalmos buttressing their contention by chemical analysis of orbits removed post mortem from patients dying with thyrotoxicosis

Muscles

Muscular weakness is commonly present in Graves disease and may though only rarely be associated with severe atrophy of the muscles The exact pathology of the muscles in this disease is not known since few muscle biopsies have been performed Patients dying of thyrotoxicosis however have shown atrophy and degeneration of muscle cells fatty infiltration loss of striations vacuolization proliferation and nuclear degeneration Thorne [7] has reported similar changes in the muscles of patients who have died with so called chronic thyrotoxic myopathy The heart muscle does not show these changes or in fact any specific alteration

Experimentally it has been shown by Paulson [63] that thyrotrophin administered to guinea pigs will produce degenerative changes in skeletal cardiac and ocular muscles These changes are characterized by an initial reaction of diffuse Zenker s degeneration associated with infiltration of phagocytes giant cells and lymphocytes later this is replaced by atrophy and separation of the fibers an increased number of nuclei in

the sarcolemma and lymphocytic collections Dobyns[64] has also noted that thyrotrophin will produce extensive fatty infiltration in the skeletal and ocular muscles as well as in the viscera, and that there is an associated increase in connective tissue in all tissues

Thymus, Lymphoid Tissues, and Bone Marrow

Hyperplasia of the thymus gland is frequently encountered in autopsied cases of thyrotoxicosis It may rarely be demonstrated as a substernal shadow in chest roentgenograms of patients with thyrotoxicosis Generalized lymphoid hyperplasia is even more constantly found with manifestations in the Peyer s patches of the small intestine and in the solitary glands in the large bowel The Malpighian bodies of the spleen show hyperplasia similar to that found in status lymphaticus There may occasionally be slight increase in splenic size and generalized lymph adenopathy

The pathology of the bone marrow in Graves' disease has been well studied by Jones[65] and Bistrom[66] utilizing sternal aspiration Little correlation was found between the bone marrow and the peripheral blood picture The latter is commonly characterized by a lymphocytosis of both absolute and relative proportions moderate over-all leucopenia is frequent In the bone marrow, Jones reported myeloid hyperplasia Bistrom similarly found hyperplasia and a definite increase in the number of young neutrophilic and eosinophilic granulocytes as well as increased numbers of immature red cells He regarded this shift to the left as a form of maturation arrest which ran rather parallel to the severity of the disease and which he ascribed to the high levels of metabolism

Bones

The relation of the thyroid hormone to mineral metabolism has been discussed in Part 1 Extensive and severe decalcification may occur owing to the high calcium losses which are characteristic of thyrotoxicosis This finding is not constant depending on the age of the patient, the duration of the disease, and the dietary intake of calcium and vitamin D

Liver

Patients dying of severe thyrotoxicosis show a high incidence of pathological change in the liver, ranging from fatty infiltration through vari

ous stages of hepatitis and cirrhosis to necrosis and atrophy[6, 53, 61, 70, 71] These changes are not specific and are associated with the varied factors *of undernutrition emaciation hypovitaminosis and hypermetabolism* which are characteristic of fatal hyperthyroidism

Liver biopsies obtained by aspiration in the course of Graves disease have shown slight and atypical changes[7] even in severe cases indeed the majority showed no anatomical change Clinical and biochemical evidences of hepatic insufficiency are more commonly seen this will be discussed in the section on pathological physiology

Pituitary

In spite of the abundant evidence indicating that the thyrotrophin of the anterior pituitary is an important regulator of thyroidal function *as well as bearing a probable relationship to the development of exoph* thalmos pathological material substantiating these interrelations in human thyrotoxicosis is very scanty The largest autopsied series is that of Holst[73] who reviewed seventeen cases of his own and fourteen cases from other clinics The pituitary was normal or decreased in size never increased The basophils were found degenerated with no constant changes in the eosinophils These findings are consistent with pituitary hypofunction clearly a paradoxical situation in hyperthyroidism emphasizing our lack of knowledge of the etiology of Graves disease

Parathyroids

The excessive excretion of calcium in hyperthyroidism has occasioned interest in the relation of the parathyroids to this process As pointed out in Part 1 there is lack of agreement concerning the presence of hyperparathyroidism in thyrotoxicosis The evidence pro and con has been largely based *on clinical or biochemical studies without regard to* pathological change in the parathyroid glandules themselves Histo pathological studies are important because hypersecretion of the para thyroids is associated with characteristic changes which exhibit themselves as diffuse hyperplasia benign solitary adenoma and rarely as malignant adenoma Little has been published *on the subject of parathyroid his* tology in Graves disease With the assistance of Dr William B Ober we have investigated[74] the material available in our clinic This material consisted of 52 single parathyroid glands removed deliberately or acci

dentally in the course of subtotal thyroidectomy for diffuse toxic goiter All the patients in this series were actively thyrotoxic and had been prepared for surgery with the usual course of iodide therapy None showed clinical or biochemical evidence of hyperparathyroidism In 46 of the 52 cases the single parathyroid gland available was entirely normal In the remaining 6 cases, however, there was variable enlargement of the gland up to twice the normal size, caused by moderate increases in the number of oxyphil cells in the glands One of these 6 cases showed marked oxyphil hyperplasia The significance of these findings is not clear

Pathological changes in the adrenals, gonads, and pancreas are inconstant and not characteristic

Clinical Manifestations of Graves Disease and Their Pathological Physiology

This section will deal with the manifestations of toxic goiter that can be comprehended through clinical examination in conjunction with those laboratory aids which have become an indispensable part of thyroid diagnosis and which may rightly be regarded as extensions of the physician s capacity to see and feel

Goiter

The thyroid gland exhibits moderate enlargement in most instances however there are patients with such slight or minimal enlargement that the goiter may be overlooked The enlargement is symmetrical and diffuse with firmness of the thyroid tissue and clear outline of the borders and lobes The surface is generally smooth or finely lobulated The position of the goiter is that of the normal thyroid occasionally lower, almost never substernal except when associated with nodules The size of the gland is not significantly correlated to the severity of the disease The hyperplastic thyroid has increased vascularity, this is manifested by the presence of thrills and murmurs, more commonly found in the superior poles The murmur is usually systolic but may be of the to and fro type with a definite diastolic component Non toxic enlargements of the thyroid or hyperplastic glands which are not hyperfunctioning rarely show murmurs or thrills so that these signs are important in suggesting the diagnosis of thyrotoxicosis

Eye Signs

The ocular changes of thyrotoxicosis are most commonly associated with classical Graves disease rather than with toxic nodular goiter except in those instances where the nodules have resulted from involution of a pre existing diffuse toxic goiter Woods has divided the eye signs of toxic goiter into four general groups as follows (a) lid signs (b) external changes in the lids or eyes (c) extra ocular palsies and proses and (d) exophthalmos The lid signs and the external changes in the lids or eyes may occur in non toxic or toxic nodular goiter but are more common in the toxic diffuse type Extra ocular palsies proses and exophthalmos are characteristic of toxic diffuse goiter

a Lid Signs

1 Dalrymple s sign refers to widening of the palpebral fissure on fixation of the eyes and is caused by retraction of the upper lid It is seen in about one half the cases of toxic goiter It produces the characteristic stare which is frequently mistaken for exophthalmos The retraction of the upper lid does not interfere with closure of the lids

2 *von Graefe s sign* or lid lag consists of the lagging of the lid behind the downward excursion of the eyeball Occasionally the lid fails entirely to descend as the eye is depressed The lagging descent of the lid exposes a narrow to broad rim of sclera above the cornea Repeated trials may be necessary to elicit this sign Lid lag occurs early in the disease and is found in over three fourths of the cases It is independent of exophthalmos and may be abolished by drugs affecting the nervous system such as morphine

3 *Stellwag s sign* refers to the infrequency of winking which may occur in thyrotoxicosis It accentuates the staring expression but is not a common sign

4 *Joffroy s sign* describes the failure of the forehead to wrinkle upon upward rotation of the eyes—the frontalis does not contract concomitantly with contraction of the levator of the lids

These signs depend on an imbalance in the opening and closing mechanism of the lids Normally the muscles involved in these processes are the levators of the upper lids innervated by the oculomotor or third cranial nerve which raise the upper lids and the orbicularis oculi innervated by the facial or seventh cranial nerve which close the lids These two muscles normally contract and relax in the synergistic fashion of

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Exophthalmos is always present though it may not be readily apparent unless measured with the exophthalmometer Control of the thyrotoxicosis brings about recession of the paralysis We have seen an instance of this type of palsy in a patient with moderate thyrotoxicosis and an initial BMR of plus 50 per cent The thyrotoxicosis was completely remitted by the administration of potassium iodide with slow but complete disappearance of the ocular paralyses after a period of 1 months Throughout this period the patient was held in a state of latent thyrotoxicosis by the iodide until natural remission had occurred Subtotal thyroidectomy or any other measure that effectively abates the hyperthyroidism will also alleviate the weakness of the eye muscles

The cause of these ocular palsies is not known Though associated with exophthalmos this cannot be the true cause since high degrees of exophthalmos can exist without any paralysis Organic changes in the muscles themselves as demonstrated by muscle biopsy are rare in this group[7]

The second group of ocular palsies are distinguished by the severity of the associated exophthalmos rather than by involvement of the extraocular muscles Brain has termed the condition exophthalmic ophthalmoplegia Jensen[11] has described it as malignant exophthalmos and Means[8] has referred to it as hyperophthalmopathic Graves disease Rundle[7] prefers to call it the ophthalmic type of Graves disease The usual mildness of the associated thyrotoxicosis together with the fact that the syndrome is frequently precipitated by thyroidectomy or more rarely by medical relief of the thyrotoxicosis has led many authors to consider this syndrome as a special and separate kind of Graves disease rather than as a special kind of ophthalmopathy associated with ordinary thyrotoxicosis or as a sequel to its recession To this latter view we ourselves incline for reasons which will be elaborated

Clinically the syndrome is characterized by exophthalmos so marked that the lids cannot cover the eyes adequately There is interference with movement of the two eyes in a particular plane Exposure of the cornea leads to dryness then ulceration and eventually to destruction of the eyeball Swelling of the lids and of the conjunctivae is always present and in fact precedes the exophthalmos Reduced mobility of the eyes inco ordination of muscle function epiphora and conjunctivitis are also present The ophthalmoplegia is rarely complete but involvement of the muscle groups that elevate the eyes is common Optic neuritis may occur

As has been noted previously the eye muscles show a characteristic

opposing muscles In addition to these two voluntary muscles there are also involuntary smooth muscles in the upper and lower lids, innervated by the sympathetic nervous system These muscles influence the width of the palpebral fissure

The primary cause of the disturbances in lid closing and opening in toxic goiter is unknown though the lid signs can be simply explained in terms of the muscles involved The Dalrymple sign may be produced by a relaxed orbicularis with compensatory overaction of the levator and hypertonicity of the involuntary lid muscles producing a wide palpebral fissure The lid lag of von Graefe may result from tonic contraction of the palpebral smooth muscles Relaxation or atony of the orbicularis would produce Stellwag's sign An overactive levator with a lack of synergistic action by the frontalis would lead to Joffroy's sign

b External Changes in the Lids and Eyes

Under this heading are included the following (1) weakness of convergence or Moebius sign (2) abnormal pigmentation of the skin of the lids or Jellinek's sign and (3) excessive lacrimation None of these signs is common or important diagnostically and their mode of production is uncertain

c The Extra ocular Palsies

These occur in about 0 3 per cent of all cases Woods [75] has classified the extra ocular palsies into two groups (1) single or multiple palsies associated with severe thyrotoxicosis and exophthalmos which improve following subsidence of the hyperthyroidism, (2) single or multiple palsies associated with exophthalmos and with mild thyrotoxicosis, which do not subside but in fact become aggravated as the disease remits

There are many exceptions in each of these two groups, in our experience since the first group of palsies may be associated with mild or moderate thyrotoxicosis is not necessarily conjoined with exophthalmos and may not entirely recede after amelioration of the hyperthyroidism The second group of palsies has become known as exophthalmic ophthalmoplegia or as the hyperophthalmic form of Graves' disease While it is generally true that the associated hyperthyroidism is mild thyrotoxicosis of moderate or severe degree may be present

The ocular palsies of the first group may affect any of the various eye muscles individually or in groups and may be unilateral or bilateral Diplopia and inability to move the eyeball freely are the chief symptoms

or pseudo exophthalmos In relative exophthalmos the eyeball protrudes relative to its previous position but is still in a range that is normal for some individuals In absolute exophthalmos the degree of protrusion is of an order that is abnormal for any eye In normal persons the distance from the external orbital margin to the anterior surface of the orbit is 1 to 16 mm as measured on an accurate exophthalmometer such as the Hertel Myopia per se may cause some degree of exophthalmos Measurements over 16 mm in the absence of high myopia are absolutely indicative of exophthalmos From 16 to 6 mm is the usual range of measurements found in the exophthalmos of Graves disease It is clear that an eyeball which normally protrudes 12 mm and protrudes 14 mm in association with thyrotoxicosis has become exophthalmic by measurement if not by clinical observation The average increase in protrusion of the eyeball in Graves disease is about 5 mm as compared with 7 mm in exophthalmic ophthalmoplegia [8] In false or pseudo exophthalmos the marked stare caused by extreme retraction of the upper lid gives an impression of exophthalmos which is not borne out by measurement with the exophthalmometer In such instances a correct clinical evaluation may often be made by examination of the eyes after gentle closure of the lids

The incidence of exophthalmos in Graves disease varies considerably it is obviously present in at least half of all cases but its true incidence is uncertain because of inadequate examination with the exophthalmometer Very rarely exophthalmos either bilateral or unilateral may be the first manifestation of Graves disease [7] preceding significant elevations of the basal metabolism or other clinical signs however the rarity of this occurrence should be emphasized since ordinarily exophthalmos appears simultaneously with the rest of the characteristic signs and symptoms of the disease Contrary to the general belief that exophthalmos recedes when the hyperthyroidism is brought under control Grace and Weeks [8] and Soley [91] found little or no recession of exophthalmos during a five year period after remission of the thyrotoxicosis Soley [91] in fact found increases of 1 5 mm in exophthalmos after treatment in half of the cases The disappearance of lid lag and stare led earlier observers to the erroneous conclusion that exophthalmos itself had decreased *Soley s observations lend further support to the belief that there* is an etiological relationship between thyrotoxicosis either present or pre existing and exophthalmos and that depression of the metabolism to normal or subnormal levels tends to increase the exophthalmos

The pathogenesis of exophthalmos in toxic goiter has been discussed

pathology—chronic hypertrophic myositis with fibrosis, edema, and lymphorrhages These organic changes probably account for the ocular palsies

The cause of exophthalmic ophthalmoplegia is not known, but the conditions under which it occurs indicate some possible mechanisms of causation Though it does occur in the course of thyrotoxicosis it is more likely to be precipitated or become progressive following thyroidectomy [58, 79, 80, 81] or the remission of thyrotoxicosis after treatment with thiourea derivatives [6] It has been claimed that the syndrome may occur in patients with euthyroid function who have never been thyrotoxic A critical survey of the reported cases has failed to substantiate this contention in our opinion Mild hyperthyroidism is readily overlooked particularly if the basal metabolism is not evaluated, Brain [78] for example determined the basal metabolism in only 8 out of his 31 reported cases Of these 8, 6 had elevated basal metabolisms, 2 were reported as within normal limits but exact figures are not offered Thyrotoxicosis may be present when the basal metabolic rate is elevated to an extent considered within the normal range by some Furthermore the pathological picture of the resected thyroid glands described in Brain's report is not inconsistent with involutionary changes induced by iodides in a hyperplastic gland An occasional case of spontaneous myxedema has been found associated with malignant exophthalmos [83, 84] but this has not occurred in our clinic In fact myxedema induced in patients with intractable heart disease by total ablation of the normal thyroid gland or through the use of radioactive iodine has not once been followed by exophthalmos in the large series of well over 150 cases studied by H L Blumgart [8] at the Beth Israel Hospital in Boston

Exophthalmic ophthalmoplegia is far more common in males than in females this is particularly striking in view of the high incidence of exophthalmic goiter in females Marine [86, 87] found that exophthalmos induced in rabbits by methyl cyanide was more common in young male rabbits and was prevented by castration

We incline strongly to the view that pre-existent or co-existing thyrotoxicosis is an essential element in the cause of progressive severe exophthalmos and that unknown factors in the interplay between the thyroid gland and the anterior pituitary are largely responsible for the ophthalmopathia of Graves' disease

d Exophthalmos

This manifestation of Graves' disease may be seen as relative absolute

metabolically and clinically The moist warm flushed skin occurs because the hypermetabolism requires the increased elimination of heat This is accomplished through vasodilatation Sensible sweating and insensible perspiration are both increased The skin temperature particularly in the lower extremities is elevated [94] in order to promote heat loss Increased perspiration both sensible and insensible is also a reflection of this same necessity The insensible perspiration representing water vapor from the lungs and skin and carbon dioxide from the lungs is increased proportionately to the basal metabolism [94] The rate of blood flow through the extremities has been found significantly increased in hyperthyroidism [9] The number of patent capillaries has also been found to be significantly greater in the skin of hyperthyroid patients [96] All of these changes are quickly reversed by medical or surgical control of the disease

Subjectively the patient will complain of excessive warmth and increased sweating or these complaints may be readily elicited by questioning There will be preference for cooler weather and varying degrees of heat intolerance or thermophobia Dermographia and urticaria are frequently seen Increased pigmentation is common in long standing cases as is vitiligo which may occasionally be found in combination with an Addisonian type of pigmentation [97] A rare dermal syndrome called localized myxedema or circumscribed thyrotoxic myxedema has been reported by several authors [9, 98] It is characterized by mucinous deposits within non pitting raised bluish yellow rectangular plaques occurring in the lower extremities The condition appears to have no relation to true myxedema It usually occurs after thyroidectomy for toxic goiter although it has been initiated by thiouracil induced euthyroidism and has also occurred during active thyrotoxicosis

Abnormal pigmentation of the nails may occur during thyrotoxicosis with disappearance upon remission [35] Nutritional disturbances associated with toxic goiter result in trophic changes in the nails longitudinal striae may appear and eventually there may be flattening or even spooning of the nails as in marked cases of hypochromic anemia

The hair is characteristically fine and silken in Graves disease but in long standing cases it may be dry and lusterless It usually becomes thinned from excessive falling out

Nutritional State

Maintenance of the body weight depends on a balance between energy

by Woods[75], its relation to thyrotrophin or a related exophthalmic factor in the anterior pituitary has been reviewed in Part II. Many concepts have been advanced to explain the exophthalmos. Hyperplasia of the orbital contents, especially of the fat, was first advanced by Basedow[4] as a possible cause of exophthalmos. This hyperplasia does indeed exist and is the immediate cause of the protrusion of the eyeball.

A second theory ascribes the exophthalmos to overactivity of the cervical sympathetic, which produces its effect by contraction of Mueller's orbital muscles. In man this muscle covers the superior aspect of the infra-orbital fissures and acts to tense the fascia of the floor of the orbit. In animals where the muscle is less vestigial, it is conceivable that its contraction could cause exophthalmos. In man, however, a direct stimulation of the cervical sympathetics under carefully controlled conditions has failed to result in any measurable protrusion of the eyeball[9]. In any event this factor cannot be significant in view of Soley's observations[91] on the permanence of established exophthalmos in thyrotoxicosis. Orbital hyperplasia obviously cannot result instantly from nerve stimulation.

Edema of the orbital contents, dilation of the orbital blood vessels and the occurrence of degenerative myositis with increased muscle bulk have also been advanced as possible causes of exophthalmos. None has been convincingly established as the primary factor, though all are present to a degree and may therefore be considered contributory.

The theory that the anterior pituitary elaborates a hormone, perhaps thyrotrophin or a closely related secretion, which causes exophthalmos is attractive and better substantiated than all others for animals. In man, however, little is yet available beyond theory. So we can only agree with Woods[7] in his final conclusions, as follows:

The problem is still unsolved. Exophthalmos is probably not related directly to thyrotoxicosis and not at all to sympathicotonia. Both thyrotoxicosis and exophthalmos are related in some way to the action of anterior pituitary hormone. The means by which it accomplishes this end is still a mystery. Muscular action probably cannot pull or push forward the eyeball. Orbital hyperplasia and edema with myositis are present but it is not clear whether these changes are primary or follow displacement of the eye. Once initiated, however, this orbital hyperplasia persists and may progress despite control of the thyrotoxicosis.

The Skin, Nails, and Hair

Changes in the skin are of particular importance in toxic goiter, both

conserving mechanism does not operate and the basal metabolism remains high or may even go higher. If inadequate calories are ingested, weight loss occurs; this weight loss necessarily represents combustion of body tissue, first available carbohydrate, then surplus fat and finally protein. In thyrotoxic patients who have lost or who are losing weight, respiratory quotients of about 0.75 will be found, indicating that the body is consuming its own fat depots to supply the total calories demanded by the organism.

The caloric requirements for weight maintenance in toxic goiter may be enormous and are usually proportional to the basal metabolism. Boothby and Sandiford[1], as well as Sturgis and Greene[101], have estimated that the total energy requirement may be as high as 100 per cent above the basal level, in contrast to an average increase of 50 per cent in normal persons. What this means in calories for a 24 hour period may be readily seen from the figures of Boothby and Sandiford[10], who showed that in thyrotoxic patients at rest in bed a 24 hour caloric intake of 3517 calories was necessary for weight maintenance or slight weight gain, an intake 90 per cent greater than the average basal caloric requirement in euthyroid subjects.

Jones[104], in a study of self selected diets in various diseases, has demonstrated that patients with toxic goiter uniformly tend to select a diet rather low in protein and high in carbohydrate. Nutritionally this type of selection may be harmful, but metabolically it may be justifiable since it represents another way of reducing the specific dynamic action of food which resides largely in the protein fraction.

Cardiovascular Manifestations

The cardiovascular manifestations of toxic goiter are palpitation, tachycardia, dyspnea, arrhythmias, increased blood pressure, overactivity of the heart, various physiological murmurs, cardiac enlargement and heart pain. These symptoms and signs are largely due to the alterations in cardiovascular physiology caused by excessive thyroid hormone. Autopsies of patients dying from hyperthyroidism have shown no characteristic lesions; mostly the hearts are normal except where there has been co-existent heart disease[3], particularly rheumatic and coronary heart disease. Although McEachern and Rake[10] feel that hyperthyroidism can cause cardiac hypertrophy, Hurxthal[106] found normal sized hearts by roentgenography except where there was coincident cardiovascular

taken in as food and energy expended through the oxidative processes that make up the basal metabolism plus increments of varying size produced by work specific dynamic action of foods and changes in temperature Regulation of the amount of food ingested depends on the appetite whereas the regulation of energy expenditure depends initially on the level of the basal metabolism In toxic goiter the nutritional state is significantly altered because there is on the one hand a marked increase in appetite and on the other hand, slight to marked increases in the basal metabolism These factors are opposed in their physiological effect but in this disease the appetite fails to maintain the body weight in the face of persistent and increasing elevations both in the basal and total metabolism

The increased appetite so characteristic of thyrotoxicosis is not so apparent to the patient as to the family and friends who notice the excessive consumption of food If questioned the patient readily admits the increase of appetite but rarely offers it among the chief complaints Anorexia occurs in very ill patients particularly in those on the verge of crisis but may be seen in any phase of the disease Sturgis and Greene [101] found moderate to marked increases in appetite in 55 per cent of their cases a normal appetite in 33 per cent and a decreased appetite in the remaining 12 per cent This analysis indicates that in at least one third of the cases the patient had not been aware of subjective changes in the desire for food

Weight loss in toxic goiter is one of the commonest symptoms noticed by the patient The factors involved have been studied by Boothby and Sandiford [10] and by Sturgis and Greene [101] A normal person will have a total caloric need about 50 per cent above the basal caloric requirement This is represented chiefly by muscular exertion and to a smaller extent perhaps 10 per cent, by the specific dynamic action of food In toxic goiter however there is present in addition the factors of body tremors inefficient utilization of muscular contraction in work [101] and a considerable increment in the percentage of calories ascribed to specific dynamic action of food because of the large food intake When these extra burdens are superimposed on the higher level of basal metabolism which obtains in the disease it is apparent that the maintenance of normal body weight is difficult and usually impossible either when the disease is moderate or severe or when it is mild and protracted

Weight loss and undernutrition in euthyroid persons will result in quite marked reduction in the basal metabolism—which tends to counteract further decreases in weight In thyrotoxic individuals, however this

brought about by the increased volume output of the heart the decreased diastolic pressure results from the peripheral vasodilatation characteristic of the disease

The *increased pulse rate and pulse pressure* together with the flushed warm moist skin indicate that the rate of blood flow is increased in toxic goiter The minute volume output of the heart in thyrotoxic patients at rest corresponds to that in normal individuals doing light work [116, 117, 118, 119] In general the basal cardiac output is proportional to the basal metabolism in hyperthyroidism increases of from 50 to 100 per cent may therefore be found *A contributory factor in the production of the increased output may be the rapid flow of blood from the arterial to the venous side through widely dilated thyroid vessels characteristically found in the hyperplastic gland of Graves disease* Rynearson and his co workers [illegible] found an oxygen saturation characteristic of arterial blood in both the thyroid artery and vein in thyrotoxicosis indicating an extremely patulous capillary bed in the gland itself allowing rapid passage of blood A similar condition prevails in the peripheral capillary bed so that in hyperthyroidism the increased work of the heart is expended chiefly upon the increased frequency of the pulse rate rather than in overcoming mechanical obstruction to the flow of blood Yater [illegible] believes that this reduced resistance in the peripheral capillaries to blood flow explains the infrequency of heart failure and cardiac hypertrophy *in spite of the increased cardiac work which obtains in toxic goiter*

Blood volume itself is increased in thyrotoxicosis according to Gibson and Harris [illegible] The velocity of blood flow or the circulation time is markedly accelerated both in the systemic and the pulmonic circuits This has been amply demonstrated by the employment of objective tests as in the radioactive deposit method of Blumgart and his co workers [illegible] or by the use of a variety of tests utilizing subjective end points after injection of such drugs as sodium dehydrocholate [illegible] and calcium gluconate [illegible] The increased velocity of blood flow in toxic goiter is probably one of the responses to the needs created by an elevated metabolism

The *heart is characteristically overactive in Graves disease* This is *manifested by the forceful and diffuse cardiac impulse the increased intensity of the heart sounds and the presence of physiological murmurs* The slapping and prolonged character of the impulse frequently gives the impression of an early systolic thrill An accentuated first sound at the mitral area and a loud second sound at the pulmonic area are usually found with thyrotoxicosis The mitral first sound is not only loud but

disease Friedberg and Sohval[107] in their series of 27 autopsied cases of Graves disease found that cardiac hypertrophy was uncommon in uncomplicated thyrotoxicosis and that when present it was of slight degree Cardiac dilatation, however may occasionally occur and will be marked if there is heart failure

The direct action of thyroxine on the heart muscle is responsible for much of the disturbed cardiac physiology Lewis and McEachern[108] showed that the isolated hearts of thyroxinized rabbits continued to beat at a faster rate than similar preparations from normal animals Andrus and McEachern[109] and Yater[110] confirmed these observations and found that the accelerated rate might persist for hours to days after withdrawal of thyroxine Similar findings in the dog have been reported by Priestley Markowitz and Mann,[111] who transplanted the heart of a small dog into the neck of a larger animal and demonstrated marked acceleration of rate in the transplanted heart from injected thyroxine

Palpitation is one of the most frequent presenting symptoms of thyrotoxicosis but because of its subjective nature is of less diagnostic significance than tachycardia Consciousness of heart action in thyrotoxicosis is due not only to tachycardia but also the increased force of the heart beat the widened pulse pressure and increased cardiac output

Pulse rate in toxic goiter generally parallels the basal metabolism This correlation is more exact when the pulse rate is determined under resting basal conditions Means and Aub[112] noted a parallelism between the pulse rate and the metabolism in hyperthyroidism Sturgis and Tompkins[113] found a similar correlation in a study of 154 patients with toxic goiter and concluded that resting pulse rates below 80 were rarely associated with an increased metabolism A study of their figures however indicates many exceptions to this trend It has been our experience also that resting pulse rates below 80 may occur in toxic goiter of mild or moderate degree The tachycardia of thyrotoxicosis persists during sound sleep[114] unlike tachycardias ascribable to psychogenic factors

Pulse pressure is increased in thyrotoxicosis chiefly as a result of a moderate elevation of the systolic blood pressure and a slight lowering of the diastolic component[112] Patients in the older age groups may have arterial hypertension associated with their hyperthyroidism In such instances the effect on the pulse pressure is similar to that which occurs in thyrotoxicosis unassociated with hypertension Control of the hyperthyroidism usually results in lowering of the pulse pressure due to a decrease in the systolic component and a slight elevation of the diastolic pressure The increase in systolic blood pressure in toxic goiter is

Transient heart block either complete or with marked prolongation of the auriculo ventricular conduction time has been reported in association with toxic goiter This is a rare manifestation for not over a dozen cases have been reported [130] but its probable relation to excessive thyroid hormone is indicated by the reported development of transient complete heart block following the ingestion of large doses of desiccated thyroid [131]

These cardiac disturbances are similar to those observed during the course of acute infections particularly with regard to their paroxysmal nature and the reversion to normal with control of the toxemia or infection Cardiac hypertrophy is rare or slight indicating that overwork of the heart is not the sole factor causing these disturbances although in thyrotoxicosis there is increased cardiac work A toxic factor perhaps the direct effect of excessive circulating thyroid hormone is probably of great importance in their etiology

Dyspnoea is not commonly presented as a symptom of uncomplicated thyrotoxicosis but is readily acknowledged when the patient is questioned It is due both to the reduced vital capacity that is characteristically found in Graves disease [133 134 135] and to the large oxygen needs of the tissues

Neuromuscular Manifestations

Nervousness irritability restlessness increased fatigability tremors and muscular weakness are common complaints in toxic goiter

The *nervousness* of Graves disease is more apparent to the observer than to the patient It is not uncommon for the patient to feel overly optimistic even euphoric and to deny nervous symptoms However many are irritable react quickly with excessive tears or laughter to trivial stimuli and on observation present a picture of mild to severe agitation There is loquacity and rapid almost eruptive speech The patient is restless carries out many unnecessary movements usually jerky and unco ordinated but purposeful and associated with considerable tremor of the hands sometimes of the entire body Though appearing to be emotionally labile the patient often exhibits a great drive and desire for work which cannot be accomplished with facility because of the increased fatigue that is characteristic of the disease Most patients are exceptionally intelligent and anxious to co-operate but frequently show poor judgment and lack of appreciation of the degree of their illness Cerebral activity is increased and insomnia is common

snapping in quality and simulates closely the final component of the late diastolic crescendo murmur of mitral stenosis

Cardiac murmurs are common and are generally of two types both systolic in time (1) a blowing systolic murmur of variable intensity which accompanies the first sound, lasting through part or all of systole heard at the mitral area with a variable transmission toward the axilla depending upon its loudness, and (2) a blowing systolic murmur localized at the third left intercostal space Both these murmurs disappear with remission of the thyrotoxicosis When the mitral systolic murmur is loud, transmitted toward the axilla and associated with a snapping first sound the diagnosis of mitral stenosis and regurgitation may strongly suggest itself Indeed structural disease of the mitral valve cannot be excluded in such instances until the thyrotoxicosis has abated Diastolic murmurs of the heart have not occurred in our experience but Eason[17] has described a faint early diastolic murmur along the left border of the sternum which he considered of functional origin

The diagnosis of coexistent heart disease although difficult at times must be made as early as possible because of the deleterious effect of even mild thyrotoxicosis upon a damaged heart When the diagnosis cannot be made because of the equivocal nature of the murmurs, other considerations such as heart size associated hypertension or coronary heart disease and the presence of persistent auricular fibrillation and congestive failure will be helpful in establishing the diagnosis of heart disease

Disturbances in *cardiac rhythm* occur commonly in toxic goiter These comprise sinus arrhythmias extrasystoles paroxysmal tachycardia, paroxysmal or persistent auricular fibrillation auricular flutter, and heart block The most frequently encountered arrhythmia is auricular fibrillation with an incidence of 15 to 25 per cent Paroxysmal fibrillation is more characteristic of thyrotoxicosis but persistent fibrillation may become established in the older age groups or when there is associated heart disease Occasionally it may be an early and marked manifestation of hyperthyroidism appearing in paroxysmal form while the disease itself is mild or not clearly apparent[18] yet in other cases permanent fibrillation may precipitate heart failure of such degree as to obscure completely the underlying thyrotoxicosis[19] Transient fibrillation may be provoked by acute infections or by surgical procedures occasionally serving to direct attention to a previously overlooked toxic goiter

Auricular flutter occurs in rare instances and is usually transitory In the few cases reported there has been no evidence of associated heart disease[18, 179]

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Exceptionally there may be asthenia and even marked prostration rather than nervousness and irritability This is seen most commonly in the group of elderly patients with long standing thyrotoxicosis

Tremor is a fairly constant manifestation of Graves disease It is generally evident in the outstretched hands or in the tongue and is accentuated by effort While usually fine and rapid with eight to ten vibrations per second it may be so coarse as to suggest Parkinsonism particularly when it is widespread Choreiform movements are occasionally present and may persist even in sleep Muscular inco-ordination may be associated with the tremor and interfere with walking

Muscular weakness is likewise characteristic of Graves disease showing itself particularly in weakness of the quadriceps femoris muscles with inability to step upon a high stool or to maintain extension of the leg for a normal period of time Buckling of the knees may occur with an increased tendency to fall Muscular cramps and joint pains may occur

Physiologically the muscle weakness and tremors are probably related to the disturbance in creatine metabolism that occurs in thyrotoxicosis This has been discussed in Part 1 and in this chapter in the section on pathology It will receive further consideration in the section on complications of toxic goiter under the heading of thyrotoxic myopathy Muscular and nervous fatigue resulting from the persistently elevated metabolism is undoubtedly an important causative factor similar to the tremor produced in normal individuals by excessive exertion In any case all of these neuromuscular manifestations disappear following adequate control of the thyrotoxicosis

Gastro intestinal Manifestations

Thyrotoxicosis may produce the following gastro-intestinal symptoms looseness of the bowels diarrhea nausea vomiting and abdominal pain The *looseness and frequency* of the bowels are probably due to the hypermotility of the gastro intestinal tract that occurs in a majority of patients Shirer[136] in a roentgenographic study of 4[illegible] cases demonstrated such hypermotility in 76 per cent of the cases with a marked decrease following thyroidectomy Lerman and Means[137] as well as Berryhill and Williams[138] have found a considerable incidence of histamine anacidity in patients with Graves disease but this anacidity is not characteristic since many thyrotoxic individuals have an associated peptic ulcer with hyperchlorhydria

Though looseness or frequency of the bowels is common *diarrhea* of severe degree is uncommon except as a precursor of thyrotoxic crisis or as a feature of severe cases with avitaminoses or chronic malnutrition

Anorexia followed by *nausea* and marked *vomiting* with or without diarrhea also occurs as a precursor of crisis or in the crisis itself or as a manifestation of severe toxicity When extreme it may be mistaken for acute intestinal obstruction Iodides administered intravenously or orally will readily control these symptoms

Abdominal pain of a degree and character as to mimic an acute surgical abdominal illness has occurred several times in our experience and has been reported by Robertson Wohl and Robertson[139] as well as by various continental authors The differential diagnosis is very difficult since the syndrome is rare and the thyrotoxic patient may have an associated gastro intestinal lesion Iodides orally or intravenously will cause rapid amelioration of the symptoms in two or three days and thus may be helpful in the differential diagnosis The cause of this type of abdominal pain in toxic goiter is not clear but it probably is due to the metabolic upheaval and coincident chemical changes in the peritoneum Similar abdominal pain is occasionally seen in diabetic acidosis and in the crisis of adrenal cortical insufficiency

Hematological Manifestations

In the section on pathology in this chapter the characteristic changes in the bone marrow were described These consist of a *myeloid hyperplasia* with an increased number of young granulocytes and immature red cells The peripheral blood reflects none of this disturbance in the bone marrow but does exhibit special features in Graves disease A slight *depression of the total leucocyte count* is common and is associated with *an absolute and relative increase in the number of lymphocytes* with a decreased number of neutrophils[9] This tendency to *leukopenia* and *neutropenia* may be confusing in following patients under treatment with thiouracil or its derivatives Treatment with iodides is usually followed by a return to a more normal hemogram

The tendency to *lymphocytosis* in Graves disease has not been found by all investigators Hertz and Lerman[140] utilizing a supravital staining technique found a *relative and absolute monocytosis* characteristic of the blood of their patients with exophthalmic goiter They found the absolute number of lymphocytes to be normal

Anemia by itself, is uncommon in thyrotoxicosis especially in view of the active bone marrow Pernicious anemia in association with thyrotoxicosis has been reported,[141] [14] however and we have observed it ourselves in two patients Three fourths of the 76 reported cases had hyperthyroidism before the development of pernicious anemia Both diseases require their own specific treatment for remission

Gonadal Function in Graves' Disease

The interrelations of the thyroid and the gonads have been discussed in Part II There it was pointed out that excessive thyroid administration inhibited normal ovarian development in the growing rat that the thyroid gland was essential for proliferation of the mammary ducts, that thyroxine enhanced the stimulant effects of progesterone and estrogen upon the growth of lobular and alveolar tissue in the breast and that thyroid gland substance would cause duct proliferation and hyperplasia of the end buds of the breasts in male mice

Clinically, amenorrhea scanty menstrual flow, or decreased frequency of menstruation are common in thyrotoxicosis With severe hyperthyroidism amenorrhea is common, and with this may come atrophy of the breasts if the amenorrhea persists for more than three or four months Associated undernutrition and avitaminosis are undoubtedly important additional causative factors in this decreased gonadal function

In the male, gynecomastia may occur as well as impotence and loss of libido even in cases of moderate thyrotoxicosis Gynecomastia usually disappears with control of the hyperthyroidism [143] The gynecomastia may be caused by a direct effect of excessive thyroxine upon the breast or may be secondary to depressed testicular function which is thought by some to initiate gynecomastia [144] In thyrotoxicosis the 17 ketosteroid excretion in the urine may be decreased indicating a depression of adrenal cortical or testicular function of both [145]

METABOLIC ALTERATIONS IN TOXIC GOITER

Basal Metabolism

The role of the basal metabolism in the diagnosis of thyrotoxicosis has already been discussed (see Part V) It may be stated axiomatically that the basal metabolism is invariably elevated above the normal for the

particular patient when the hyperthyroid state supervenes With the standards now in general use the basal metabolism in toxic goiter will range from plus 5 to plus 100 per cent not very many patients will fall in the range from plus 5 to plus 10 per cent though Means[349] has reported about 5 per cent of cases to be within this range In our experience any patient with a basal metabolism slightly but persistently on the plus side should be carefully scrutinized for the possibility of hyperthyroidism About three fourths of all cases will have basal metabolic levels between plus 20 and plus 60 per cent

As a test for the exclusion of thyrotoxicosis the basal metabolism is entirely dependable — truly normal values or minus values determined *in a reliable test absolutely exclude the disease The converse is however* not true — elevated values do not establish the diagnosis since other diseases particularly arterial hypertension malignant lymphoma and heart disease will also cause hypermetabolism in the demonstrated absence of thyroid hyperfunction

While the relationship of the basal metabolic level to the degree of thyroid toxicity is variable there is considerable parallelism since high rates generally indicate severe thyrotoxicosis and slight or moderate elevations of the rate accompany slight or moderate degrees of the disease Of course other factors must be considered in the evaluation of the level of toxicity but a well established level of basal metabolism *is an excellent guide to the degree of toxicity* the progress of the illness and the effect of therapy

Iodine Metabolism in Toxic Goiter

The increased secretion of thyroid hormone is the fundamental biochemical alteration in toxic goiter While the mechanism responsible for this hypersecretion is unknown there is considerable knowledge concerning the factors necessary for hormone production hormone inhibition and hormone delivery to the blood stream and peripheral tissues The normal iodine metabolism particularly as it relates to hormone synthesis and the structure of the thyroid gland has been described in Part IV and in the section on biochemistry of Part I Leaving aside morphological considerations one may succinctly state that the thyroid gland synthesizes thyroid hormone by the iodination of tyrosine to form diiodotyrosine followed by *the coupling of two diiodotyrosine molecules* to form thyroxine Both iodination and coupling are apparently oxidative reactions necessitating oxidation of iodide entering the thyroid

gland The steps involved in the iodination of tyrosine are imperfectly understood but recent experiments of Fink and Fink[147] and others[147, 148] utilizing radioiodine have indicated that this iodination may take place in several stages the first being the addition of one atom of iodine with the formation of monoiodotyrosine This chemical formulation makes it clear that inhibition of either iodination or coupling will suppress hormone synthesis In addition any agent that prevents access of iodine to the gland will have a similar effect

The selective absorption of iodine by the normal thyroid gland is therefore a mechanism that supplies the thyroid cells with a basic material for hormone synthesis The relative ease with which radioactive iodine can be traced in man has afforded considerable understanding of the pattern of accumulation and discharge of iodides in the thyroid gland Stanley and Astwood[148] have demonstrated that the rate of accumulation of radioactive iodine by the thyroid gland during the first few hours after its administration may be expressed as an approximately straight line by plotting the square root of the elapsed time against the number of counts per second the latter as the ordinates the former as the abcissae of the graph Though newer techniques of measurement of radioactive iodine[149] will permit an exactly quantitative measurement of the percentile uptake of a given dose of radioactive iodine by the gland the method of Stanley and Astwood has proved very useful in the study of the iodine metabolism of the human thyroid They demonstrated in man[150] as had Chaikoff and his co-workers in the rat[151] that the antithyroidal goitrogens derived from thiourea do not prevent access of considerable quantities of radioactive iodine to the thyroid gland, even with virtually complete inhibition of hormone synthesis The administration of thiocyanate or ordinary iodide in large amounts effected prompt but not complete discharge of this collected radioactive iodide from the thyroid gland since most of it was not organically bound because of the blocking effect of the antithyroidal compound Thiocyanate in addition to effecting a rapid discharge of iodide accumulated in the gland while under the influence of propylthiouracil also prevents entry of iodide into the gland itself by a blocking mechanism (see Part III) The completeness with which previously accumulated radioactive iodine disappears from the thyroid gland depends on the dose of thiocyanate or potassium iodide and on the potency of the precedent antithyroid medication In toxic goiter there is a larger uptake of iodide than in normal persons and the discharging effect of thiocyanate or stable iodine on this accumulated iodide is much more rapid and abrupt than in the normal but it is not as complete

Radioactive iodine is rapidly released from the thyroid by large doses of potassium iodide when the gland itself is under the influence of an antithyroid compound because the stable iodide saturates the gland to a point where the gradient between the body fluids and tissues and the thyroid itself is sharply reduced

Stanley and Astwood concluded from their studies[14, 15] that an increased ability of the thyroid to concentrate iodide ion was correlated with hypertrophy or hyperplasia of the thyroid This histological response has repeatedly followed the administration of thyrotrophin in the experimental animal In human subjects Stanley and Astwood[15] found that injected thyrotrophin in as pure a form as obtainable for clinical use caused a marked acceleration of iodine uptake by the thyroid after an initial and inexplicable lag of about 8 hours there ensued a high uptake which was maximal in 4 to 48 hours falling to normal after 4 or 5 days This ability of thyrotrophin to increase the iodide concentrating capacity obtained both in the normal gland and in the gland whose capacity to synthesize hormone had been completely inhibited by antithyroidal compounds of the thiourea series Thyrotrophin appears to enlarge the iodine space of the thyroid either by increasing uptake of iodide ion as demonstrated in man by Stanley and Astwood or by promoting hormone synthesis through iodination and coupling as has been shown in animal and in vitro experiments (see Part II)

The transport of iodine to the thyroid gland as well as the delivery of hormonal secretion to the peripheral tissues takes place by way of the blood stream Iodine on its way to the thyroid gland is carried in the plasma as inorganic iodide and as such has an important regulatory effect on thyroid function according to Wolff and Chaikoff[133, 134, 135, 136] The organic binding of iodine within the thyroid gland which is another way of saying iodination of tyrosine to form diiodotyrosine and coupling of diiodotyrosine to form thyroxine can be almost completely inhibited by sufficiently raising the level of inorganic iodide in the plasma This blocking however is not permanent and when the plasma inorganic iodide level drops below a critical level hormone synthesis resumes This suggests a natural homeostatic mechanism for controlling the formation of thyroid hormone and preventing excessive hormone production after a large intake of iodine While high levels of inorganic iodide in the plasma will block hormone synthesis they do not interfere with the ability of the gland to concentrate iodine in inorganic form

The demonstration in the normal rat of the inhibitory effect of excessive plasma inorganic iodide upon the synthesis of diiodotyrosine

and of thyroxine has supplied an additional explanation of the effect of iodine therapy in thyrotoxicosis This explanation is based on the assumptions that inhibition of hormone synthesis by excess iodide occurs (1) in man and (2) in the thyrotoxic gland of man Both of these assumptions have yet to be proved An objection to this theory is the fact that only a small number of patients with thyrotoxicosis will show sufficiently complete or prolonged inhibition of hormone synthesis from large continued doses of iodides to produce a euthyroid state In other words in the vast majority of cases there is partial remission with iodides inferentially indicating partial blocking of hormone production or release In addition reduction of thyroid function in the euthyroid individual to hypothyroid levels has not been achieved by the administration of large doses of iodides

We agree with Wolff and Chaikoff [154] that 'an interference in organic binding of iodine by the gland is an integral part of the mechanism by which iodine brings about a remission in Graves disease' Iodine acts additionally in this disease however by decreasing the amount of thyroid hormone delivered to the blood stream thus indirectly promoting hormone storage Means and Lerman [157] consider that large doses of iodide block delivery of hormone from the gland This is manifested clinically by a decrease in thyrotoxic symptoms and chemically by a fall in the level of circulating hormone as measured by the protein bound iodine of the blood As this process continues the iodine content of the thyroid increases and this increase is due to actual hormone storage as manifested by a steadily rising content of bound iodine first as diiodotyrosine and later as thyroxine or a thyroxine-like fraction After 10 to 14 days the percentage of thyroxine iodine reaches the normal value of ~6 per cent of the organic iodine Iodine treatment in Graves disease therefore establishes an approach to the normal pattern both in the gland and in the blood stream converting the iodine poor colloid deficient thyroid to a gland with abundant organic iodide stored as newly formed colloid Concomitantly the hormonal iodide of the blood decreases Salter [158] considers that the essential action of iodide in toxic goiter is to reverse the direction of hormonal flow at least temporarily

It is clear from the foregoing discussion that the mode of action of iodide in toxic goiter is complex inasmuch as it has been thought to have such opposite effects as inhibition of hormone synthesis increase of hormone storage and decrease of hormone delivery or discharge McClendon Foster and Cavett [159] have pointed out that the thyroglobulin of the thyrotoxic gland is abnormally low in thyroxine — one

case for instance showing values of 0 0046 per cent thyroxine as compared to the normal value of 0 3 per cent thyroxine They feel that the beneficial action of iodides in Graves disease is caused by an increase in the protein bound iodine of the pituitary gland and thus inferentially of its thyroxine content This locally increased thyroxine inhibits thyrotrophin release from the pituitary thus resulting in decreased excretion of thyroid hormone from the thyroid gland itself A postulation of increased intrapituitary thyroxine is not in any event needed since elemental iodine and iodides in vitro will inhibit thyrotrophic activity (see Part ii)

The Thyroid Clinic of the Massachusetts General Hospital has offered a two action theory to explain the effect of iodine in toxic goiter [161] It is pointed out by this group that minute amounts of iodine are essential for hormone synthesis and this role of iodine is termed its iodinating action In the normal gland iodine in excess of this amount will be excreted iodine below this amount will result in an iodine want type of goiter In toxic goiter there is rapid hormone production which results in increased iodine avidity Excess iodine administered under these conditions effects involution of the gland and detoxification of the patient This action of iodine is termed its involuting action and it is precisely this effect that is obscure

The two action theory is founded upon the differential effect of thiouracil and iodide administered simultaneously to patients with Graves disease Thiouracil inhibits hormone synthesis or iodination while it increases hyperplasia Iodide however promotes involution in the same gland which when inhibited is not capable of iodinating or synthesizing hormone Thus iodide exerts the double action of iodination and involution It was concluded that the involuting effect of iodide was exerted through inhibition of thyrotrophin which resulted in decreased thyroid cell activity and a block in hormone delivery

The action of iodine in thyrotoxicosis appears to be both on the pituitary and on the thyroid itself the latter action has been more firmly established in man both clinically and experimentally The two action theory has demonstrated simply that morphological involution may occur without significant hormone formation Colloid presumably stored thyroglobulin forms when both iodine and thiouracil act upon the hyperplastic gland of Graves disease This thyroglobulin must necessarily have a low content of thyroxine and in this respect is similar to the thyroglobulin found in untreated thyrotoxicosis So far as the thyroid gland is concerned one may therefore recognize two types of iodine

effect with the same histological picture of involution (1) involution with a normally iodinated thyroglobulin and (2) involution with thyroglobulin of low hormone content In either case there is clinical improvement and occasionally complete arrest of the disease

Iodine therefore may exert its effect in Graves disease in any or all of the following ways

(1) by inhibition of hormone formation through maintenance of high plasma levels of inorganic iodide (Chaikoff *et al*),
(2) by the reversal of direction of cell secretion (Salter)
(3) by blocking hormone discharge from the gland (Means *et al*),
(4) by the production (with thiouracil) of a hormone deficient thyroglobulin,
(5) by inhibition of thyrotrophin formation either through (a) direct action of iodine on thyrotrophin with inactivation or (b) indirect suppression of thyrotrophin secretion through the presence of *increased amounts of thyroid hormone within the pituitary* itself (McClendon *et al*)

Thyroid hormone and inorganic iodides whether in the normal or the thyrotoxic individual are carried by the blood stream to the peripheral tissues and cells where the hormone exerts its definitive action In several of the preceding Parts the nature of the circulating hormone has been discussed The accumulated evidence points strongly in our opinion to the fact that the mobile form of the hormone is thyroxine While *Taurog and Chaikoff*[171] *feel* that circulating *thyroxine is loosely* attached to plasma protein Salter[16] has adduced evidence to indicate that the binding of thyroxine by plasma protein may be a firm one since hormonal iodine in a normal plasma precipitates with acetone, whereas thyroxine added to the plasma of myxedematous individuals will not so precipitate

The protein bound iodine in the plasma is unevenly distributed among the protein fractions of the plasma most of it residing in the albumen fraction although the alpha beta globulin fraction *contains the most* iodine per gram In patients with profound hypo albuminemia Peters[113] has found levels of protein bound iodine in the blood as low as in myxedema These patients have shown no signs of hypothyroidism and administration of either effective doses of thyroid or enough human albumen to raise the serum albumen considerably has produced no rise in the protein-bound iodine In conditions associated with marked hypoalbuminemia therefore the protein-bound iodine level of the blood will *not be the accurate index of thyroid function that ordinarily* obtains

Radioactive thyroxine has been utilized to trace the course of thyroxine when it is administered intravenously. Gross and Leblond[104] have demonstrated that radioactive thyroxine disappears rapidly from the blood stream after intravenous injection. This disappearance is not due to inactivation or destruction by the blood since thyroxine loses none of its activity after in vitro incubation with blood. Thyroxine is actually withdrawn from the blood by various organs and tissues, especially the liver. The liver in turn excretes up to 90 per cent of the injected dose into the gastro-intestinal tract where it is finally lost in the feces. Much of the thyroxine is excreted unchanged through the bile and possibly some of it is broken down with the liberation of iodide. Little thyroxine is excreted in the urine but there is an increased iodide elimination as the result of thyroxine degradation. The pituitary gland of the rat fixes no thyroxine, although that of the rabbit has been shown by Horeau and Sue[105] to fix considerable quantities of thyroxine.

Protein Metabolism in Toxic Goiter

The characteristic abnormalities of protein metabolism in thyrotoxicosis have been considered in the section on physiology in Part I. It was pointed out that urinary nitrogen is increased in the disease because of increased protein catabolism; nitrogen balance, however, is attainable as in the normal when adequate calories are provided by carbohydrates and fats. The state of nitrogen balance has no influence on the disturbed creatine metabolism that generally occurs in toxic goiter.

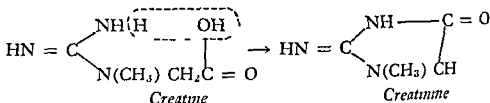
Muscle Weakness

Muscle weakness is an important symptom of toxic goiter and rarely may be of such extreme degree as to constitute a distinctive myopathic syndrome. As such it will be discussed under the complications of toxic goiter. The altered physiology underlying muscle weakness in thyrotoxicosis, however, requires further consideration.

Hypercreatinuria is a relatively constant finding in Graves' disease, so constant that many investigators have proposed it as a diagnostic test. In this connection due regard must be had for the fact that creatine is normally present in the urine of prepuberal children of both sexes, frequently in women, almost continuously in pregnancy, and in both men and women under the following conditions: high protein diet, star-

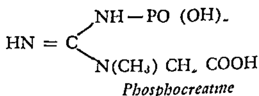
vation, carbohydrate lack, diabetes, and wasting diseases, as well as in certain muscular dystrophies In thyrotoxicosis there is (1) increased creatinuria (2) decreased amounts of creatinine in the urine, and (3) a decreased capacity to metabolize ingested creatine is measured by urinary excretion While there is divergence of opinion as to the cause and degree of alteration of creatine metabolism in toxic goiter, there is every likelihood that the excessive creatine excretion reflects changes in muscle function and structure

There are about 120 grams of creatine in the human adult and 98 per cent of this is contained in the muscles where it is probably formed and where it undergoes (by dehydration) conversion into creatinine at a remarkably constant rate in accordance with the magnitude of muscle metabolism



Creatine *Creatinine*

Creatine itself is synthesized from glycine arginine, choline and methionine The kidney conjugates arginine and glycine to form glycocyamine or guanido acetic acid[166] This latter is methylated in the liver[167] through a methyl group contributed by choline and methionine About 30 per cent of the creatine remains free but the remainder is phosphorylated in the muscle to form phosphocreatine[168]



Phosphocreatine

Phosphocreatine functions in the muscle as the source of the phosphate groups in adenosine triphosphate The dephosphorylation of the latter to adenosine diphosphate and adenylic acid apparently supplies the energy for muscular contraction Re synthesis of adenosine diphosphate and adenylic acid to adenosine triphosphate is accomplished through the phosphate group of phosphocreatine

Creatinine represents the end product of creatine metabolism and is

formed by simple loss of a molecule of water from creatine at a uniform rate – per cent daily of the total body creatine

The explanation of the disturbed creatine creatinine metabolism in toxic goiter is unclear Iodine administration rectifies the metabolic error in Graves disease but has no effect in the creatinuria of non thyrogenous myopathies[169] Shorr considers the abnormality to reside in an impaired capacity of the muscles to withdraw creatine from the blood and also suggests that there may be impaired efficiency in the re synthesis of adenosine triphosphate phosphocreatine with reduced stores of both[170] Thorn[171] agrees with Shorr that there is a fundamental disturbance in creatine metabolism in toxic goiter Other investigators, however espe cially Tierney and Peters[17] and Wilkins and Fleischmann[174] do not find evidence of abnormal creatine metabolism merely facilitation of creatine loss from muscles

Carbohydrate Metabolism and Liver Function in Toxic Goiter

The role of the thyroid gland in carbohydrate metabolism has been discussed in Part 1 and it was there pointed out that the thyroid hormone had a fourfold effect (1) it is partly diabetogenic and capable of depress ing or abolishing insulin secretion in animals whose insulin production has been lessened by damage to or reduction in the number of pancreatic islets (2) it causes marked acceleration in the rate of intestinal absorp tion of glucose (3) it depletes liver and muscle glycogen but does not interfere with glycogen formation or storage if adequate calories and vitamins are ingested and (4) it increases carbohydrate utilization in the tissues

If the thyroid hormone is in part diabetogenic and does indeed acceler ate intestinal absorption of dextrose one would expect to find (1) a worsening of established diabetes (2) a precipitation of frank diabetes in mild and unsuspected cases and (3) post prandial hyperglycemia and glycosuria in non diabetics Actually thyrotoxicosis seriously intensifies existent diabetes uncovers the mild diabetic and causes clinical dis turbance of carbohydrate metabolism in the non diabetic

Glycosuria

Glycosuria in slight to moderate degree is found in the great majority of patients with Graves disease when systematic examinations are car

ried out [174] This glycosuria is invariably post prandial and is due chiefly to the rapid absorption of dextrose that occurs in thyrotoxicosis There is slight lowering of the renal threshold for dextrose in some cases and this too contributes in part to the glycosuria The blood sugar curve following the ingestion of dextrose in thyrotoxicosis is frequently increased in height at the end of one hour, tending to rise above the normal renal threshold of 170 to 180 mg After this sharp rise the heightened curve may be increased in duration or may more typically drop sharply to normal at the second hour and exhibit moderate hypoglycemia at the third hour Fasting blood sugar values may be elevated up to 20 mg above the normal by thyrotoxicosis alone but fasting values above 150 milligrams are generally due to associated diabetes

The role of the liver in the abnormal carbohydrate metabolism occurring in Graves disease is indicated by the abnormal galactosuria and marked elevation of blood galactose levels which are found after the ingestion of a test dose of galactose in most patients This sugar cannot be utilized until it is converted to dextrose by the liver [17] Machella Helm, and Charnoch [176] studied liver function in a small group of patients with hyperthyroidism, both uncomplicated and associated with heart disease They found little impairment of hippuric acid synthesis or retention of bromsulphalein dye except in the group with co existent heart disease

Fatal cases of Graves disease may show marked lesions in the liver characteristics of hepatitis as pointed out in the section on Pathology in this chapter Fatal thyrotoxicosis with its attendant hyperthermia and other severe metabolic derangements is both qualitatively and quantitatively so different from the usual non-fatal case as almost to represent another disease In most patients with thyrotoxicosis clinical and laboratory evidence of severe hepatic impairment is found only when there is thyrotoxic crisis associated congestive failure, or cirrhosis of the liver The clinical evidence of disturbed liver function rests largely on the occasional finding of jaundice in hyperthyroidism This has occurred chiefly in patients with heart failure or in patients with crisis who have developed acute yellow atrophy

Alteration in Fat Metabolism in Toxic Goiter

The effect of thyroid function upon lipid metabolism has been considered in the section on physiology in Part 1 There it was noted that

hypothyroidism produced abnormal elevations in the blood lipids far more regularly than thyrotoxicosis produced abnormally depressed values While the blood cholesterol is used as a convenient laboratory index of the blood lipids careful fractionation has shown that hyperthyroidism may depress not only the cholesterol but also the fatty acids cholesterol esters and phospholipids It was also pointed out that cure of the thyrotoxic state was usually associated with some rise in the blood cholesterol level The lowering of blood cholesterol by thyrotoxicosis probably occurs with as much regularity as its elevation by myxedema but the decrease may not be appreciated because the shift is not as marked and tends to remain within the wide normal limits of blood cholesterol values whereas in myxedema the increase is characteristically beyond the normal range

Vitamin Metabolism in Toxic Goiter

The influence of the thyroid hormone upon vitamin metabolism has been reviewed in Part 1 The two vitamins whose metabolism is most regularly influenced by disturbed thyroid function are Vitamin A and the B vitamins Hyperthyroidism increases the need for Vitamin A In severe avitaminosis A in rats the thyroid gland is increased in size owing to increased colloid deposition which is associated however with degenerative changes in other parts of the gland The uptake of radioactive iodine by such glands is normal but the incorporation of this iodine into diiodotyrosine to form thyroxine is significantly slowed[177]

Sadhu and Truscott[178] have found that rats with hypervitaminosis A had a decrease in the protein bound iodine content of the liver and thyroid but an increase in the serum pituitary and skeletal muscles Simkins[179] utilized massive doses of Vitamin A (up to 400 000 units daily) in the treatment of two patients with toxic goiter and apparently effected complete remission of the thyrotoxicosis within several weeks thus confirming the earlier experience of Wendt[180] The clinical use of massive doses of Vitamin A as a means of controlling hyperthyroidism needs further study

The B vitamins that are particularly related to thyrotoxicosis are thiamine pyridoxine pantothenic acid and probably riboflavin The needs of these vitamins are proportional to the amount of food metabolized and thus may be increased with elevation of the total energy metabolism Williams and his co workers[181] have shown that patients with Graves

disease tend to have low or subnormal blood levels of both free thiamine and co-carboxylase the biologically active form of thiamine This low blood level was ascribed to excessive urinary excretion as well as to increased oxidation of food There is abundant evidence of an increased need for pantothenic acid and pyridoxine in experimental hyperthyroidism Clinically ariboflavinosis is rare in thyrotoxicosis, in our experience

Mineral Metabolism in Toxic Goiter

The urinary and fecal excretion of both calcium and phosphorus is strikingly increased in thyrotoxicosis and eventually leads to varying degrees of osteoporosis if the negative calcium balance is not corrected by a high calcium intake or cure of the disease The mechanisms of this increased excretion are discussed in Part I In elderly patients osteoporosis may be marked and associated with pathological fractures In such patients cure of the thyrotoxicosis does not always correct the osteoporosis because of the additional factor of absent or declining gonadal function with secondary decalcification Treatment with sex hormones may therefore be necessary in such instances

As pointed out in Part I in the section on mineral metabolism there is an increased amount of bound magnesium in the serum of most patients with toxic goiter, according to some investigators This finding however has failed of confirmation by other workers We have not measured the serum magnesium in our cases

Clinical Course of Graves Disease

The *natural history* of thyrotoxicosis is difficult to trace since in the modern period when adequate and objective tests have been available medical and surgical treatments have intervened to alter the primary disease in a beneficial or pejorative fashion The earlier studies of Plummer,[18] Barker [183] Dunhill [184] Eason [1 7] and Joll [35] all point to a conclusion that is in accord with our own twenty year experience—namely that thyrotoxicosis is a chronic disease running a mild moderate or severe course of many years duration, exceptionally undergoing rapid or spontaneous cure at an early stage or flaring into thyrotoxic crisis with death The majority of cases are monocyclic in the sense that there is no recurrence following adequate treatment by medical or surgical methods A considerable minority however are polycyclic in their course recurring

one or more times after a complete remission which has lasted for months or years A small number of cases resist all methods of treatment and remain persistently thyrotoxic over many years One of our patients belonging in this latter group had thyrotoxicosis for 7 years and required three thyroidectomies persistent iodide administration several courses of external roentgen ray irradiation prolonged thiouracil therapy and finally three doses of radioactive iodine before control of the disease was secured Re growth of thyroid remnants to large size may be seen in this type of case and in the patient noted above the attainment



Fig 50 C R age 4 with diffuse toxic goiter of about one years duration I^{131} uptake 72 7 per cent in 4 hours PBI^{131} = 100 per cent conversion half life = 3 days PBI = 1 4 micrograms Treated with stable iodide and tapazole Complete remission in 3 months Maintained in euthyroid state with tapazole 5 mg daily

of euthyroidism has left a large disfiguring goiter which will require a fourth thyroidectomy (Figs 50 51A 51B 5)

The *mode of onset* in Graves disease is usually gradual but rarely insidious and in occasional cases it may develop suddenly over a period of days in an individual previously in good health The cases with sudden onset usually present a history of a traumatic episode associated with severe fright followed shortly thereafter by the appearance of the characteristic signs of Graves disease As we have indicated earlier for

thyrotoxicosis to develop the psychic stimulus must impinge upon the readied personality with its inherited predispositions In cases of more gradual onset, associated with subacute states of anxiety or grief or other types of emotional disturbance, it is not entirely clear whether the disturbed emotions precipitate thyrotoxicosis *de novo* or exacerbate an



Fig 51 A T S (BIH No 83661A) Woman age 21 with diffuse toxic goiter Note exophthalmos and large symmetrical goiter B M R was plus 52 and plus 53 per cent Treated with I 131 receiving 3.0 mc on 10/5/47 3 0 mc on 1/12/48 and 5 3 mc on 3/15/49 Hypothyroid since May 1949 when B M R was minus 29 per cent Is now on 0 130 gm desiccated thyroid daily

already existent Graves disease In the closely studied series of Fitz[193] which consisted of 33 patients personally followed over many years the majority of which were observed before the development of hyper thyroidism 27 patients had a gradual onset and 6 patients a sudden onset There were no discernible precipitating factors in 24 of the patients with

gradual onset the remainder in this group developed thyrotoxicosis in association with either a respiratory infection or rheumatic heart disease In the 6 patients with sudden onset one followed severe psychic trauma two followed respiratory infections one followed an attack of asthma one occurred with the climacteric and one occurred without discernible cause



Fig 51 B Profile view

In our own experience both in the clinic and in private practice the acute onset following traumatic episodes is rare but the gradual onset associated with a variety of emotional disturbances is increasingly common as the history is probed with more care and insight Lidz and Whitehorn[183] have stressed the occurrence of serious emotional crises before the onset of Graves disease and consider that thyrotoxic patients as a group because of childhood insecurities are particularly sensitive to the loss or threat of a loss of a cardinal interpersonal relationship

Characteristic of the gradual onset of Graves disease in the patients with mild toxicity is an excessive sense of well-being, an anomalous euphoria which may confound the observer into the diagnosis of neurosis



Fig 52A M F (BIH No 99191) A 51 year old woman with persistent diffuse toxic goiter since 19 0 First thyroidectomy in 19 2 Two other thyroidectomies since then for persistent thyrotoxicosis and regrowth of thyroid remnants Has also had two courses of external radiation and prolonged treatment with iodides and thiouracil I^{131} therapy finally abolished the thyrotoxicosis but patient still has large regrown goiter Appearance on 3/15/48

Clinically *the intensity of the disease* may range from the severe through the moderate and mild to the latent or incompletely remitted forms The severe form is usually associated with basal metabolic rates

above plus 60 per cent with a history of marked weight loss and accentuated thyrotoxic symptoms plus physical findings of extreme restlessness very vascular goiters marked tachycardia tremors and sweating The mild cases may present clear cut symptoms or may be so asymptomatic



Fig 52 B Profile view

that only the observation of increasing irritability or exophthalmos by friends or relatives brings them to the physician In this group the basal metabolism is generally below plus 30 per cent and may hover just above the normal limits with occasional readings in the normal range that is

Characteristic of the gradual onset of Graves disease in the patients with mild toxicity is an excessive sense of well being an anomalous euphoria which may confound the observer into the diagnosis of neurosis



Fig 5 A M F (BIH No 99191) A 51 year old woman with persistent diffuse toxic goiter since 1920 First thyroidectomy in 19 2 Two other thyroidectomies since then for persistent thyrotoxicosis and regrowth of thyroid remnants Has al o had two courses of external radiation and prolonged treatment with iodides and thiouracil I131 therapy finally abolished the thyrotoxicosis but patient still has large regrown goiter Appearance on 3/15/48

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Fig 52 I Profile view

that only the observation of increasing irritability or exophthalmos by friends or relatives brings them to the physician In this group the basal metabolism is generally below plus 30 per cent and may hover just above the normal limits with occasional readings in the normal range that is

from plus 5 to plus 10 per cent The great majority of the patients fall into the group of moderate toxicity, averaging from plus 25 to plus 60 per cent in their basal metabolism with characteristic signs and symptoms of unmistakable degree The moderate and severe groups are rarely diagnostic problems, the mild cases frequently require a higher degree of clinical awareness for their recognition

In many patients with pre-existent heart disease and in the elderly the clinical picture may be masked either by congestive failure or by a lack of reactivity amounting to apathy, weakness, and somnolence

An important group of cases with Graves' disease comprises those patients who are held in complete clinical and metabolic remission by iodides or antithyroidal drugs but who promptly flare into active thyrotoxicosis with omission of these drugs It is clear that in these patients the morbid stimulus within the patient has remained ready to act as soon as the inhibitory effect of the antithyroidal agent is removed This stimulus is as it were temporarily 'locked up or confined and prevented from exerting its force Yet eventually after months or more commonly, years rarely decades the stimulus disappears and the disease burns itself out This concept of drug induced latency is both important and useful since it directs attention to the true nature of Graves' disease particularly its remarkable capacity to persist for many years even though all its manifestations are suppressed

The Diagnosis of Graves' Disease

The diagnosis of Graves' disease may be simple or difficult depending on the degree to which the characteristic symptoms and signs are present In the typical case the classical symptoms of palpitation nervousness hyperhidrosis thermophobia increased appetite and weight loss combined with exophthalmos, goiter tachycardia and tremor make the diagnosis self evident Laboratory tests will be confirmatory and are indicated chiefly as an objective *measure of the* level of thyrotoxicosis In cases that are atypical mild or border-line however the diagnosis may be difficult to establish and may require not only a full complement of laboratory tests but prolonged clinical observation as well, and occasionally a test of the therapeutic effectiveness of iodide administration

The border line or mild cases of hyperthyroidism may be a diagnostic problem because the patient is euphoric and presents few, if any complaints until directly questioned Furthermore, some patients will have

symptoms suggesting psychoneurosis such as non exertional palpitation nervousness fatigue or irritability without other characteristic symptoms of thyrotoxicosis If eye signs are minimal or absent and the goiter is small the physician either may not determine the basal metabolism or may ascribe slight elevations of the basal metabolism to 'nervousness

The patient with atypical Graves disease does not necessarily have the disease in a mild form Exophthalmos may be slight the goiter small anorexia or constipation may be presenting symptoms or there may be no weight loss because of an adjustment of caloric intake to metabolic demands An atypical case associated with heart disease hypertension or alcoholism presents special difficulties, which will be discussed in the differential diagnosis

In all types the clinical signs or symptoms may fluctuate to a degree that will confuse the diagnosis and therefore require objective tests for evaluation The simplest of these is the determination of the pulse rate when the patient is in a basal or resting state The correlation between pulse rate and metabolic rate in toxic goiter has been discussed In thyrotoxicosis the basal pulse rate remains high whereas in the neuroses it is usually normal In heart disease however particularly aortic stenosis or heart block complicated by hyperthyroidism the basal pulse rate may be slow or normal A normal basal pulse rate does not by itself exclude thyrotoxicosis, it merely decreases its likelihood

The determination of the *circulation time* as a measure of thyroid function has been described in Part v It is a valuable test in co operative patients and can be readily performed after a preliminary rest period to secure basal conditions Anemia and fever also increase the velocity of blood flow In addition the range of normal function and of thyrotoxicosis may overlap This test does not measure thyroid function directly and therefore is not conclusive

The laboratory tests that have proved most helpful in the diagnosis of Graves disease have been discussed in Part v These tests are the following (1) the determination of the basal metabolism (2) the measurement of the hormonal or protein bound iodine of the blood and (3) the utilization of radioactive iodine to trace the pattern of iodine uptake and excretion of the thyroid gland The basal metabolism is a measure of the effect of the thyroid hormone on heat production whereas the protein bound iodine indicates the amount of circulating thyroid hormone The uptake and excretion of radioactive iodine delineate the size of the 'iodine space in the thyroid gland the rate at which that space is filled or emptied and the capacity of the gland to retain iodine for

hormone synthesis From a theoretical standpoint the protein bound iodine in the blood should be the most accurate diagnostic index of thyroid function In practice this has actually proved to be the case The technical difficulties of the procedure however have prevented its wider use in the clinic

The *basal metabolism test* is readily available and is unquestionably the simplest and most reliable screening test for hyperthyroidism If properly performed tests show persistently normal values the diagnosis of thyrotoxicosis can be excluded The range of normal values fluctuates somewhat in accordance with the standards selected this is of much importance and has been considered extensively in Part v We ourselves feel unwilling to exclude hyperthyroidism in a suspected case until the basal metabolism level in good tests has been persistently demonstrated to be on the minus side

Elevation of the basal metabolism is therefore an essential feature of Graves disease This elevation must be persistent and is best demonstrated by the performance of several tests on successive days or weeks until a level is secured The occurrence of normal or minus metabolism tests with good respiratory graphs during the establishment of such levels should raise doubts as to the validity of the diagnosis Persistent hypermetabolism may of course be associated with clinical states other than thyrotoxicosis particularly hypertension lymphoma and heart disease Therefore the basal metabolism test alone is not sufficiently specific to be definitive in the border-line or atypical case

The use of *radioactive iodine in tracer amounts* constitutes an additional diagnostic method which has proved valuable in the estimation of thyroid function and therefore in the diagnosis of thyrotoxicosis By utilizing doses of approximately 10 to 100 microcuries of carrier free I^{131} the pattern of uptake excretion and fixation of radioactive iodine by the thyroid gland may be delineated by four methods (1) the measurement of the concentration in the gland by external counting with single or multiple counters (2) the measurement of the urinary excretion of radioactive iodine as an inverse index of gland uptake (3) radioautography—a photographic print made on sensitized film that has been exposed to thin slices of radioactive tissue these prints may be superimposed upon fixed tissue sections to allow accurate comparisons of histology with the degree and extent of uptake of I^{131}, and (4) the measurement of total and precipitable radioactive iodine in the blood A detailed discussion of the use of I^{131} in the diagnosis of thyroid function is presented in Parts iv and v

External Counting

The concentration of radioactive iodine in the thyroid gland may be readily measured by means of the Geiger or scintillation counter Both instruments yield answers in counts per unit of time these counts will vary a great deal depending not only on the iodine avidity of the thyroid gland but also on the sensitivity of the tube itself Different tubes yield answers so far apart that an absolute figure of counts per minute in a given case would be meaningless in the interpretation of thyroid function Therefore the range of each tube for different levels of thyroid function has to be determined However by calculating the per cent of tracer material which a given gland absorbs one can achieve an absolute value of uptake that quickly outlines the functional state of the thyroid To determine the per cent uptake with accuracy involves technical problems of tube numbers and placement which have been solved [119] By utilizing per cent uptake it is possible to classify the behavior of the thyroid gland as hyperthyroid when there is an abnormally high avidity for radioactive iodine as hypothyroid when there is greatly decreased avidity and as euthyroid when the uptake pattern lies between the two extremes

TABLE VII

THE PATTERN OF UPTAKE AND EXCRETION OF TRACER AMOUNTS OF I^{131} AS INFLUENCED BY THE STATE OF THYROID FUNCTION

State of Thyroid Function		Percentile Uptake by the Gland			Urinary Excretion in Per Cent	
		At 3 hours	At 24 hours	At 7 hours	At 24 hours	At 72 hours
HYPERTHYROID	Range	52-95	50-96	42-89	48	8-49
	Average	5	4	67	18.5	20.5
EUTHYROID	Range	20-33	13-3	18-40	31-0	41-77
	Average	8.5	30	32	52	60
HYPOTHYROID	Range	12-17	4.5-13	1-7	53-6	83-99
	Average	15.3	7	2	65.4	89

The actual measurement of thyroid uptake of radioactive iodine may be made at either 3 hours or 24 hours the difference not being significant as is shown in Table VII This table is based upon data gathered by A S

Freedberg and his associates in our clinic The uptake at 72 hours is, however, not quite as definitive, because of the rapid hormonal turnover of the thyrotoxic gland with a resultant excretion of radioactive iodine incorporated into thyroid hormone and a lowering of the uptake to values closely bordering the euthyroid range In the 3- and 24 hour figures there is a wide zone of separation between the lowest values of the thyrotoxic gland and the highest values of the euthyroid gland

We have found the measurement of uptake over the gland to be a most useful and reliable index of thyroid function Previous administration of iodide however whether as potassium iodide Lugol s solution syrup of hydriodic acid, iodized salt, or iodine containing dyes used for visualization of the gall bladder or kidneys will block iodine uptake by the gland giving low uptake values even with hyperfunctioning glands Similarly, we have found instances of uptakes in the thyrotoxic range in patients without thyrotoxicosis This has occurred with hyperplastic but not hypersecretory glands resulting from iodine-lack or previous administration of thiourea derivatives In one instance persistently high uptakes were observed in a patient with chronic congestive heart failure on a low salt intake without clinical evidence of thyrotoxicosis At necropsy this patient s thyroid gland showed no hyperplasia The measurement of radioactive iodine uptake has been useful in differentiating patients with non thyrogenous hypermetabolism from those with thyrotoxicosis In the former group uptake is in the euthyroid range

Similar experience with the use of radioactive iodine in the diagnosis of Graves disease has been reported by Means,[187] Salter [188] Werner [189] and Keating [190]

Urinary Excretion

Radioactive iodine is competitively trapped by the thyroid gland or excreted by the kidneys The relationship between gland absorption and renal excretion of radioactive iodine is therefore a reciprocal function, and this inverse relation is sufficiently quantitative so that one may infer the amount of absorption of radioactive iodine by measurement of the urinary excretion

In evaluating thyroid function from the urinary excretion the excretory capacity of the kidneys must receive consideration since depression of renal function may by itself increase iodine collection by the thyroid The urinary excretion has been subdivided by Keating and his associates [191] into these four quantities (1) the renal fraction, representing

the per cent of the dose of radioactive iodine excreted in the urine ( ) the disappearance rate representing the proportional rate of disappearance of radioactive iodine from the blood (3) the renal excretion rate representing the proportional rate of excretion into the urine and (4) the collection rate representing the proportional rate of disappearance into other sites than the kidney This latter is an index of the rate of collection by the thyroid and can be more accurately measured by direct observation over the thyroid with the Geiger counter

The thyroidal factors influencing the uptake of radioactive iodine will have the same effect upon urinary excretion thus hyperplastic and hyperfunctioning glands will be associated with low excretion rates However low excretion rates and high uptakes will be found in hyperplastic glands with a low iodine content from any cause without hyperthyroidism or hypersecretion of hormone

Extrathyroidal factors are equally important influences upon the urinary excretion of radioactive iodine The percentage of iodine collected by the normal thyroid varies inversely with the size of the dose collection will be large and excretion small with minimal doses such as are employed in tracer studies Similarly renal failure whether primary or secondary to congestive heart failure or other causes will delay the excretion of iodine and afford a more prolonged opportunity for gland uptake

McArthur and her associates [19] at the Massachusetts General Hospital report the mean urinary excretion values of radioactive iodine as follows (1) in thyrotoxicosis 5 per cent with a range of 7 to 45 per cent ( ) in euthyroid subjects 60 per cent, with a range of 2, to 98 per cent These figures based on 48 hour excretion studies agree fairly well with our own data based upon the 24 hour excretion of radioactive iodine (Table vii)

Radio autography

The use of *radio autography* in the diagnosis of toxic goiter has limited value since it can be applied only to excised thyroid tissue and therefore serves as a visualized indicator of the extent of iodine uptake In spite of this limitation it has had important pathological and physiological applications Radio autography of surgically removed thyroid glands has demonstrated the variation in iodine collection which may occur within a gland or nodule Hamilton and his associates [191] were the first to show by this method that hyperplastic thyroid tissue had greater iodine uptake

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our clinic by Freedberg and his associates[3] A single determination was made 4 hours after the oral ingestion of tracer doses of I^{131} and it was found that the serum of the thyrotoxic patients had significantly higher counts than the euthyroid controls However there was sufficient overlap in the values as to decrease the diagnostic usefulness of this relatively simple procedure McConahey's[19] more elaborate method of investigation yielded a pattern of greater diagnostic specificity

Response to Iodine as a Diagnostic Test

Plummer in 19 3 first described the response of patients with exophthalmic goiter to the administration of iodine[31] Since that time numerous studies have established the characteristics and nature of the iodine response in toxic goiter Until the introduction of the antithyroidal drugs and of radioactive iodine the administration of stable iodine was a necessary step in the preparation of thyrotoxic patients for thyroidectomy For diagnostic purposes however the use of iodine still has an important place in the clinical evaluation of thyrotoxicosis particularly when more intricate methods such as radioactive iodine tracer studies or the measurement of the protein bound iodine are not available

When a patient with thyrotoxicosis previously untreated is given stable iodine in any form above a minimal level there ensues a response that is characterized by a partial to complete remission of the signs and symptoms of thyrotoxicosis together with a corresponding decrease in the basal metabolism and the level of protein bound iodine in the blood The thyroid gland likewise changes remarkably and becomes firmer less vascular and more sharply outlined

The bulk of the literature on this phase of the subject is based on the administration of iodine for 10 to 14 days before thyroidectomy These data indicate that the response to iodine is rapid occurring within days it is specific and therefore will not occur in non thyrogenous hypermetabolism or in exogenous thyrotoxicosis it may lead to a complete remission which will be maintained so long as the iodine is administered but more generally causes improvement short of complete control and finally in a few cases it may effect little or no discernible amelioration of the disease It is equally established that regardless of the stage or severity of thyrotoxicosis the omission of iodine will almost invariably worsen the process and aggravate the symptoms However if iodine has been administered long enough to effect or coincide with complete arrest of

than normal thyroid tissue and that most cancers of the thyroid had little or no capacity to concentrate iodine

Radio autographic investigations of thyroid physiology have confirmed much earlier work based on more tedious chemical or histochemical methods particularly with regard to the polarity of hormone secretion Leblond and Gross[104] concluded that the acinar cells form thyroglobulin and secrete the hormone into the colloid that this process is extremely rapid occurring within minutes after radioactive iodine administration and that the secretion rate is enhanced by iodine deficient diets and thyrotrophin and slowed by hypophysectomy

Protein-bound Radioactive Iodine

The behavior of radioactive iodine in the blood as an index of thyroid function has been studied by McConahey, Keating and Power[19] utilizing orally administered radioactive iodine Two factors were investigated (a) the rate at which radioactive iodine disappeared from the blood and (b) the appearance in the blood of protein bound radio active iodine Patients with exophthalmic goiter toxic and non toxic nodular goiter carcinoma of the thyroid and with myxedema were investigated as well as normal euthyroid subjects It was found that radioactive iodine appeared in the blood stream within a few minutes in all subjects rose rapidly to a peak within 30 to 90 minutes, and then fell at a rate that was correlated with the functional state of the thyroid In hyperthyroidism the peak was reached early and the level fell more rapidly than in the euthyroid individuals In myxedema the peak was reached later and the level fell very slowly

The rate of formation of protein bound radioactive iodine also differed in accordance with thyroid function In thyrotoxicosis essentially all circulating radioactive iodine was protein-bound after about 48 hours whereas it took 96 hours for the normal and ~90 hours for the myxedematous subjects to bind organically the available radioactive iodine As would be expected therefore the rate of hormone formation was twice as fast in the thyrotoxic as in the normal and six times as rapid as in myxedema In addition the levels of precipitable radioactive iodine in the blood were much higher in thyrotoxicosis than in euthyroidism and were quite low in myxedema

The concentration of protein bound radioactive iodine has been determined in the serum of a small group of patients with Graves disease in

Our own feeling however is that apparent refractoriness can be ascribed to unobserved or unappreciated iodination of the thyroid gland by previous ingestion of the element. Studies in our clinic with radioactive iodine have shown remarkable blocking of radioactive iodine uptake by normal or thyrotoxic glands for long periods of time following the ingestion of iodine even in the trace amounts found in iodized salt. In one patient years of ingestion of saturated solution of potassium iodide for the treatment of syphilis subsequently blocked normal iodine uptake even after one year's omission of all iodides in the ingesta. Occasional patients with thyrotoxicosis have had a depressed uptake of radioactive iodine for long periods after the administration of small amounts of oral iodides and in one instance after the taking of iodized salt alone.

Differential Diagnosis of Toxic Goiter

The diseases that may be confused with toxic goiter are those which present some of the signs and symptoms of Graves' disease or which are associated with metabolic abnormalities specific to thyrotoxicosis such as hypermetabolism increased uptake of radioactive iodine or elevation of the protein bound iodine in the blood.

Arterial Hypertension

Arterial hypertension may frequently simulate Graves' disease because of the presence of hypermetabolism in a significant proportion of such patients. In addition tachycardia palpitation vasomotor instability and stare lid lag or exophthalmos is not unusual. The elevation of the basal metabolism is genuine and persistent occasionally reaching levels as high as plus 55 or plus 60 per cent [5, 4] Severe or malignant hypertension is more likely to have an associated hypermetabolism than mild or moderate hypertension. However this is not unexceptionable and we have come to regard hypertension per se as an important source of error in the differential diagnosis of thyrotoxicosis.

The hypermetabolism of hypertension will not be affected by iodine administration nor is it associated with thyrotoxic levels of protein bound iodine in the blood or with an increased uptake of radioactive iodine by the thyroid gland. Total thyroidectomy in hypertensive hypermetabolism will not drop the basal metabolism to myxedema levels even though clinical hypothyroidism supervenes [3] conversely we have occasionally

the disease then its omission will not be followed by recurrence of thyrotoxicosis or a change from the latent to the overt stage of the malady In fact the failure of the process to light up under these conditions is the crucial test of cure or complete remission

Before iodine is administered for diagnostic purpose, it is essential to establish a reasonably accurate level of basal metabolism This usually requires several tests done on successive days or weeks until the true level has been determined Thereupon iodine should be administered for a period of two to four weeks with careful observation of its effect upon symptoms pulse rate, weight and basal metabolism With thyrotoxicosis there should be prompt and decisive amelioration in symptoms and signs and a significant drop in the basal metabolism Upon conclusion of the test period the iodine may be omitted and the upswing of symptoms and basal metabolism noted during the ensuing weeks This double diagnostic procedure occasionally is required when the initial response to iodine is inconclusive

The *form of iodine* utilized either for treatment or for diagnosis is not important so long as one gives more than the minimum necessary to produce an effect Our preference is for *saturated solution of potassium iodide* given by mouth in a single dose to 10 to 15 minims (0 6 to 1 0 cc) Thompson and his associates[13] [191] have shown that at least 6 mg of iodine must be administered daily to produce a definite effect in most cases of thyrotoxicosis This corresponds to 1 minim (0 06 cc) of compound solution of iodine (Lugol s solution) or to 1/10 minim or 0 006 cc of saturated solution of potassium iodide The recommended dosage is therefore far above the critical level of effectiveness

The response to iodine administered in the manner and amount described is characteristic of patients with thyrotoxicosis However this response occasionally fails to occur in patients who have been clearly demonstrated to have the disease The explanation for this *resistance*, *refractoriness*, or *lack of response* to iodine has been varied Plummer[200] for example explained the failure of response in some patients with toxic nodular goiter on the basis that this disease was a separate entity *from* Graves disease Subsequent studies however have shown as adequate a response in toxic nodular goiter as in toxic diffuse goiter [01] Means [ ] has denied the existence of iodine refractoriness and with this we are in full agreement He ascribes apparent resistance to iodine in toxic goiter to the coincidence of a rising phase of the morbid process so that the iodine appears not to have had any effect whereas in fact it is retarding the rate of acceleration of the hyperthyroidism

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the disease, then its omission will not be followed by recurrence of thyrotoxicosis or a change from the latent to the overt stage of the malady. In fact the failure of the process to light up under these conditions is the crucial test of cure or complete remission.

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regularly elevated The level of hypermetabolism varies but is frequently in the range found in mild or moderate thyrotoxicosis [78] This hyper metabolism is not of thyroid origin however and therefore will be unin fluenced by iodide administration Studies with radioactive iodine have not yet been reported

In *polycythemia vera (erythremia)* hypermetabolism is frequent but it is not so regularly observed as in the leukemias and lymphomas Here again the cause of the hypermetabolism is not clear and iodide adminis tration is without effect

Symptoms of thyrotoxicosis as well as hypermetabolism may result from the ingestion of excessive amounts of desiccated thyroid (*thyro toxicosis factitia alimentary thyrotoxicosis or self induced hyperthy roidism*) The dosage must be fairly large well above any clinical or therapeutic level and it must be continued for several weeks before thyrotoxic levels of hypermetabolism occur [18] In this type of exogenous thyrotoxicosis hypermetabolism is associated with high occasionally enormous levels of protein bound serum iodine [11] but the response of the thyroid gland to radioactive iodine is hypothyroid with a low uptake and high urinary excretion [1] The omission of thyroid medication will be followed by a return of the basal metabolism and blood iodine values to normal In this condition as in all hypermetabolism of non thyroid origin the administration of iodide has no effect upon the basal metabo- lism

In hypertension heart disease malignant lymphoma and exogenous thyrotoxicosis the elevation of the basal metabolism represents an actual increase of oxygen consumption under the standard conditions of the metabolism test There is no artificial element of muscle tremor fever lack of relaxation or psychic disturbance to give an erroneous answer which is essentially not really basal In conditions such as the *psycho neuroses Parkinsonism* and *chronic alcoholism* the metabolism in the standard post absorptive state may be elevated but it is rarely a basal metabolism because of associated muscle tremor as in Parkinsonism or alcoholism or because of lack of relaxation or great apprehension as in the neuroses and neuro circulatory asthenia

In *paralysis agitans* and in *alcoholism* the differential diagnosis may be difficult Weakness warm flushed skin and stare are not uncommon in these conditions The basal metabolism is usually elevated in Parkinson ism but may show wide variations in the same patient from day to day with difficulty in securing satisfactory tests Abolition of the tremor with hyoscine will permit the demonstration of normal levels of metabolism

seen spontaneous myxedema in hypertensive patients associated with normal or slightly elevated levels of basal metabolism

The cause of the increased basal metabolism in arterial hypertension is unknown A few cases are due to an associated pheochromocytoma which secretes excessive epinephrin with a concomitant calorigenic effect The clinical picture may simulate Graves' disease very closely and may even include thyroid enlargement [95] Increased heart work and overactivity of the sympathetic nervous system may be the more common causes of hypertensive hypermetabolism

Heart Disease

Heart disease both with and without myocardial failure may closely simulate thyrotoxicosis and be associated with hypermetabolism Smith and Levine [96] found persistent elevation of the basal metabolism in four cases of aortic stenosis two of them with associated mitral stenosis when the patients were free of congestive failure Weight loss tremor exophthalmos and even thyroid enlargement were present No metabolic response occurred upon administration of iodide and the thyroid glands were histologically normal when examined

In patients with cardiac decompensation whatever the etiology of the underlying heart disease hypermetabolism may be an associated finding Peabody [97] and later Willius [98] have demonstrated that this increase in metabolism is attributable to the dyspnea and that it usually occurs when there is respiratory distress at rest With improvement in cardiac function the basal metabolic rate falls to normal unless there are other causes for the hypermetabolism

In the differentiation of hypermetabolism due to cardiovascular disease from thyrotoxicosis the procedures of greatest value are (1) the measurement of the velocity of blood flow, (2) the determination of the protein bound iodine in the blood (3) the measurement of the uptake *excretion and metabolic turnover of radioactive iodine* and (4) the therapeutic response to administration of stable iodine This last should not be utilized unless the second and third procedures are not available or have yielded equivocal answers since stable iodine will interfere with tracer studies with I^{131} and in large enough amounts may alter the protein-bound iodine of the blood

In the *leukemias*, both *myelogenous* and *lymphatic*, and in the group of diseases classified as *malignant lymphoma* the basal metabolism is

tration of iodides and ( ) irradiation of the pituitary Stable iodine exerts multiple effects as we have previously noted not only inactivating thyrotrophin but also blocking thyroxin production within the gland or increasing hormone storage depending upon the amount administered

In the selection of the therapeutic method considerable attention should be given to the nature of the patient as well as to the stage and severity of the disease By this we mean that consideration of the economic and social status of the patient his place of abode in relation to the physician or the clinic his personality and capacity for co operation should enter into the selection of therapy The degree of thyrotoxicosis should also influence choice of therapeutic method mild cases lend themselves safely and readily to prolonged administration of iodides or thiourea derivatives whereas severe cases or those with complications may require quick and certain relief by thyroidectomy

A third factor that inevitably needs consideration is the availability of the desired therapeutic agent to the patient All methods should have a minimum of laboratory control by basal metabolism tests Thyroidectomy necessitates a skilled surgeon and a properly equipped hospital for optimal results For the use of radioactive iodine there must be special personnel and facilities including physicists internists electronic equipment and access to the material The thiourea derivatives and stable iodine are most readily available but the former require frequent hematological examinations External irradiation of the thyroid or the pituitary require roentgenologists with the equipment and experience to carry out this form of treatment Stable iodine therapy which is universally available demands the least in the way of equipment but needs thorough understanding of its actions and its limitations

Certain general principles of treatment apply in some degree to all patients with thyrotoxicosis regardless of specific therapy These concern the *nutritional requirement* the application of *psychotherapy* and the use of *sedatives* and other measures to diminish irritability and restlessness

The *total caloric requirements* in toxic goiter are elevated both by the increased basal metabolism and by an inefficient muscular metabolism which causes a greater than normal output of energy In some patients the increased appetite insures an intake adequate to maintain weight this however is the exception and most patients need a diet that is adequate in calories This can be roughly estimated by determining the 24 hour caloric need from the basal metabolism and by adding increments that are appropriate to the patient s activity and to the decreased efficiency

The determination of the protein-bound serum iodine and the measurement of the uptake and excretion of I^{131} are decisive in the diagnosis

Chronic Alcoholism

Chronic alcoholism frequently simulates thyrotoxicosis and may be associated with slight hypermetabolism If there is an associated non toxic goiter the diagnosis is difficult Here again the metabolic level will fluctuate and will be difficult to establish There will be no metabolic response to iodide administration, the protein bound serum iodine will be normal and tracer studies with I^{131} will yield euthyroid values

Treatment of Toxic Diffuse Goiter

Adequate therapy of Graves disease should restore normal thyroid function quickly with certainty and without disabling complications which may encumber the patient for months, years, or a lifetime Treatment should stop the excessive secretion of hormone without exposing the patient to morbid and even mortal risks more serious than the disease itself Finally treatment should be as specific as possible within the limits of available knowledge of pathogenesis

These are ideal aims and dicta which emphasize the large gaps in our knowledge and the inadequacies and even dangers of treatment

Since the clinical syndrome has protean manifestations considerable flexibility must be maintained in the therapeutic program Thus cure of thyrotoxicosis too rapidly occasionally aggravates exophthalmos to a malignant degree Hyperthyroidism may be successfully managed by thiouracil derivatives or iodides but such control may lead to or leave large disfiguring goiters which will require thyroidectomy because of pressure symptoms Thyroidectomy may quickly cure but can produce serious complications such as injury to the recurrent laryngeal nerves or hypoparathyroidism Radioactive iodine is quite effective in treatment but its tendency to produce myxedema always needs consideration

The methods available for treatment consist of procedures that reduce or abolish the production of either the thyroid hormone or pituitary thyrotrophin The methods belonging in the first category are (1) the use of antithyroidal goitrogens (2) thyroidectomy (3) the administration of radioactive iodine and (4) external irradiation of the thyroid The methods that decrease thyrotrophin production are (1) the adminis

terally in critically ill patients with diarrhea this mode of administration is essential to restore nutritional balance

The control of *physical restlessness* and *inward nervousness* in thyrotoxic patients may be difficult when they are prominent symptoms In an occasional patient they foretell the advent of thyrotoxic crisis and in all patients demand quick control or a selection of therapy that will readily ameliorate the hyperthyroidism The relief of the restlessness and nervousness should proceed along these lines (1) *psychotherapy*, (2) *reduction in physical activity*, and (3) *the use of sedatives*

Psychotherapy initially may be simple reassurance emotional support from the physician adequate explanation of the symptoms with emphasis on the usually good prognosis removal of irritating personal or physical stimuli when possible and provision of a restful environment If this is not adequate or if psychotic symptoms are present the skills of a psychiatrist should be utilized for therapy and accurate diagnosis of the psychotic deviation

Reduction in physical activity is important during the initial phase of treatment This is best achieved by planning the patient s activities rather than by bed rest The work load should be reduced or abolished depending upon the patient the degree of thyrotoxicosis and the type of therapy envisaged Many patients suitably employed can go about their daily business with little alteration others need complete avoidance of work Social activities and conflicts with hostile personalities need careful supervision or restriction Marital difficulties often abound because of the irritability of the thyrotoxic patient We have seen many instances of marital disharmony ameliorated or completely abolished by control of the hyperthyroidism

The use of sedatives to control restlessness nervousness and insomnia may be approached as in any other disease Repeated small doses of barbiturates are usually adequate though associated with occasional severe skin rashes This is not uncommon with phenobarbital but since this is the most commonly used drug one may therefore expect some incidence with any of the barbiturates We prefer not to use bromides because of the frequency of skin rashes and possible confusion with iodine dermatitis when the latter drug is used in treatment

Use of Stable Iodine as the Sole Therapeutic Agent

Since Plummer [197] first conclusively demonstrated that the administration of iodine was regularly followed by diminution in the degree of

occurring in the performance of muscular work The crucial test of caloric adequacy will be that of weight maintenance and therefore frequent weighing under standard conditions is an essential observation in the treatment of the disease For patients of average size carrying on ordinary daily activity 5000 calories would not be excessive although this amount would correspond to the daily needs of a normal person performing very heavy work The *components of the diet* should consist of 1 to 1 5 gm of protein per kilogram of body weight plus enough additional calories from carbohydrate and fat to make up the balance of the needed energy requirements No set formula need be utilized for the distribution between fat and carbohydrate since this can readily follow the patient s taste Carbohydrates in large amounts are essential because of glycogen depletion in the muscles and the liver, fat is necessary for the bulk of the calories since lack of calories in the diet will further drain the body glycogen and body fat

Thyrotoxicosis increases the need for certain *vitamins*, particularly *vitamin A* and certain of the *vitamins of the B complex* Clinically one rarely sees evidence of lack of vitamin A but instances of lack of thiamin and riboflavin are not uncommon *Thiamin requirements* are proportional to the amount of food metabolized and therefore in thyrotoxicosis whether the food intake is adequate or not the thiamin needs are high and should be specifically met by the addition of vitamin supplements [13] The evidence for increased *riboflavin need* in hyperthyroidism is less clear but in patients with toxic goiter one occasionally sees cheilosis seborrheic dermatitis with smoothness and redness of the tongue *Pantothenic acid* and *pyridoxine* have been shown to be required in increased amounts in experimental thyrotoxicosis

Vitamin supplements should therefore certainly include adequate amounts of vitamin A and B complex to supply the increased need This need will diminish as the disease is brought under control so that in many instances a diet adequate in vitamins suffices The demand for *vitamins C and D* may be increased in hyperthyroidism but no unequivocal clinical or experimental evidence has been adduced for this need

The large excretion of *calcium and phosphorus* which occurs regularly and to a marked degree in toxic goiter requires the administration of enough of these minerals in the diet to maintain a positive balance Ordinarily milk is the best source of both calcium and phosphorus one quart daily sufficing in most instances

When continued diarrhea is present vitamins should be given paren

logical ability to co-operate in long-term supervision lasting over months to years. In such a group one may achieve complete clinical and metabolic remission by the daily administration of iodine. The basal metabolism should reach absolutely normal or subnormal levels and be maintained there. Clinically, the patients should achieve that state of well-being which existed before the onset of the disease. The treatment must be maintained for at least 6 to 8 months before omission of the iodine. This omission is always to be considered as a trial. If the patient is cured the basal metabolism and clinical status will remain euthyroid; if cure has not been achieved, merely latency of the thyrotoxic state, then symptoms and signs of recurrence will quickly manifest themselves within days to weeks. If adequate control had previously been obtained with iodine, then it should be readministered for an additional 6 to 8 months with further clinical and metabolic observations at monthly or bimonthly intervals. Again, the iodine should be omitted and observations carried out as before. Cure will signify itself by maintenance of euthyroidism clinically and metabolically. This process may need repeating over periods up to 10 years or longer, though most patients will remit completely and permanently within one to three years.

The dosage of iodine utilized in our clinic has been from 5 to 10 drops of saturated solution of potassium iodide daily. As noted previously, however, any other form of iodide that supplies an adequate amount of iodine may be used.

If in the initial 6- to 8-week period of observation the metabolism does not drop to slightly subnormal values or if clinical symptoms such as tachycardia, palpitation, weight loss and nervous irritability continue, then it is unlikely that iodine alone will control the disease and one should consider other therapeutic means.

Long-term studies in large groups of patients with mild to moderate thyrotoxicosis treated by stable iodine alone have not been reported, although at the Massachusetts General Hospital stable iodine has been tried in up to 10 per cent of all cases.[216] We ourselves, both in the clinic and in private practice, have utilized it under the relatively stringent conditions elaborated above and have found it frequently curative in a select group of patients. Furthermore, in our experience it has never jeopardized the patient's welfare by preventing a needed thyroidectomy if the iodine regimen was unsuccessful. This was true before the advent of the thiouracils and is even more applicable today, since these drugs may be utilized to prepare the patient for operation in the event of lack of cure by iodides. Even radioactive iodine may be utilized after failure

thyrotoxicosis, stable iodine has been regularly used in the pre operative preparation of patients for thyroidectomy, with enormously beneficial results in the reduction of surgical mortality The capacity of iodine to produce complete and persistent clinical remission and eventual cure rather than improvement or temporary remission has not received an adequate exposition The erroneous concept of iodine 'refractoriness has deterred many from the use of iodine alone in the treatment of Graves disease Some large surgical clinics, faced with moderate or severe thyro toxicosis in patients who had had too prolonged iodine therapy without adequate planning for operation at the optimal time or without adequate clinical and laboratory supervision while receiving iodine have warned against the use of iodide exclusively in any case of hyperthyroidism Nonetheless no clinic has hesitated to use iodine alone in the control of thyrotoxicosis that has persisted or recurred after adequate thyroid ectomy

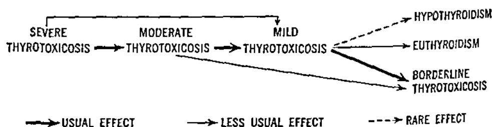


Fig 53

We have previously pointed out that iodine almost invariably reduces the degree of thyrotoxicosis at any stage of the disease Thus the severe state may be reduced to a moderate one, the moderate thyrotoxic to mild and the mild made even milder or completely euthyroid In occasional instances mildly thyrotoxic patients have even been rendered temporarily myxedemic by iodine medication alone Occasionally, too iodine will make the severe case mild or the moderate case euthyroid In general however in our experience iodine alone rarely renders the severe or moderate case completely euthyroid (see fig 53)

It is thus clear that one can frequently expect sustained remission following iodine in the group of patients who are mildly thyrotoxic and whose goiters are relatively small The degree of thyrotoxicosis should be clinically mild with little weight loss mild nervous manifesta tions and basal metabolism levels below plus 35 per cent Such patients should be further selected on the basis of their economic and psycho

logical ability to co operate in long term supervision lasting over months to years In such a group one may achieve complete clinical and metabolic remission by the daily administration of iodine The basal metabolism should reach absolutely normal or subnormal levels and be maintained there Clinically the patients should achieve that state of well being which existed before the onset of the disease The treatment must be maintained for at least 6 to 8 months before omission of the iodine This omission is always to be considered as a trial If the patient is cured *the basal metabolism and clinical status will remain euthyroid if cure has* not been achieved merely latency of the thyrotoxic state then symptoms and signs of recurrence will quickly manifest themselves within days to weeks If adequate control had previously been obtained with iodine then it should be readministered for an additional 6 to 8 months with further clinical and metabolic observations at monthly or bimonthly intervals Again the iodine should be omitted and observations carried out as before Cure will signify itself by maintenance of euthyroidism clinically and metabolically This process may need repeating over periods up to 10 years or longer though most patients will remit completely and permanently within one to three years

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th stable iodine following a waiting period of weeks to months during ich the patient may be kept partly controlled with the thiouracils Considerable time may elapse, however before a patient with thyro-cosis who has not been satisfactorily controlled with iodine is even lly rendered euthyroid by the thiouracils or radioactive iodine This t deserves emphasis both to patients and to physicians and is one of the sons why we stress the proper selection of the patient

Stable iodine has an especial usefulness in patients with *persistent or current thyrotoxicosis* and has been found curative in about 75 per cent such cases [15] Here again it is our experience that the mild case with mall goiter is more readily controlled [16] In persistent or recurrent perthyroidism where previous operation has resulted in vocal cord alysis iodine is particularly valuable Radioactive iodine may even lly supplant stable iodine in the treatment of this group of patients t pending its universal availability and final demonstration of its com te innocuousness stable iodine will remain the best therapeutic choice is safe available and effective in the properly selected patient Its ad nistration should follow the course outlined above for the treatment mild or moderate thyrotoxicosis that is prolonged administration for al periods of 6 to 8 months after which the drug is omitted One will ually learn by the initial response of the patient to iodine whether cure y be expected The development of euthyroidism or, rarely hypo roidism in one to eight weeks is a good indication of eventual cure

Occasionally persistent or recurrent thyrotoxicosis is associated with rked regrowth of thyroid remnants Iodine will usually control the rotoxic manifestations in such instances if the disease is mild or mod ite but does not prevent the growth of the thyroid remnants which casionally attain a huge size Thyroidectomy is then necessary for relief of pressure symptoms In addition, in our clinic [17] patients no regrow goiters of considerable size have had an increased incidence thyroid carcinoma

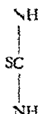
In rare instances *toxic manifestations* may be seen following iodine ministration for either short or prolonged periods *Iodine dermatitis* most commonly seen and may be severe enough to cause death [18] ch [210] has reported one case of peri-arteritis nodosa caused by hyper sitivity to iodide Most instances of iodine dermatitis are mild how er and do not require omission of iodine Reduction or, paradoxically crease of the dose may be helpful in clearing the dermatitis

We have seen instances of *swelling of the salivary glands* following the

use of iodine in toxic goiter and very rarely have noted the development of a turgidly painful goiter following prolonged iodinization

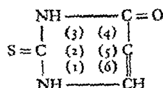
Antithyroidal Goitrogens in the Treatment of Toxic Goiter

The physiological actions and anatomical effects of the antithyroidal goitrogens have been extensively discussed in Part III The compounds that have been most applied clinically are largely derivatives of the simple *sulphur containing thiourea*



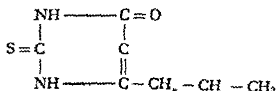
Abundant experimental and clinical studies have been made on numerous related compounds and new drugs are constantly being synthesized which are either more potent or have promise of decreased toxicity

The two drugs of widest application have been *thiouracil* and *6 N propylthiouracil* with the following structural formulas

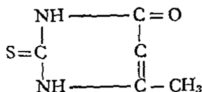


thiouracil, with the usual numbering of the atoms in its ring

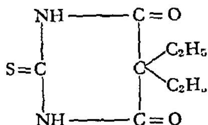
Methylthiouracil thiobarbital aminothiazole 2 mercapto imidazole and *1 methyl 2 mercapto imidazole* have all been less widely used but require discussion because of their clinical application or their presage of future developments in antithyroidal drugs



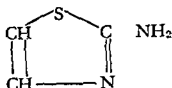
6-N propylthiouracil (propylthiouracil)



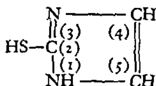
6-methylthiouracil



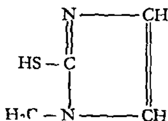
(5 5 diethyl thiobarbituric acid)
(thiobarbital)



aminothiazole



2-mercapto-imidazole



1 methyl-2 mercapto-imidazole
(methimazole ['tapazole'])

The antithyroidal goitrogens of the thiourea series exert their ameliorative effect in thyrotoxicosis by preventing the formation of thyroid hormone This inhibitory effect is biochemically specific and has been shown to prevent the addition of iodine to tyrosine for the formation of diiodotyrosine and the synthesis of thyroxine by the coupling of diiodotyrosine In large enough doses administered for long periods of time,

thiouracil and propylthiouracil have depressed hormone formation in the thyroid gland of normal individuals until myxedema has developed This has required amounts of the latter drug varying from 500 to 1500 mg given daily for many months Thus the effect of these drugs on hormone formation manifests itself in both thyrotoxic and normal glands though in different dosage

The morphological changes in the thyroid gland produced by these compounds are similar and comprise increased vascularity hyperplasia

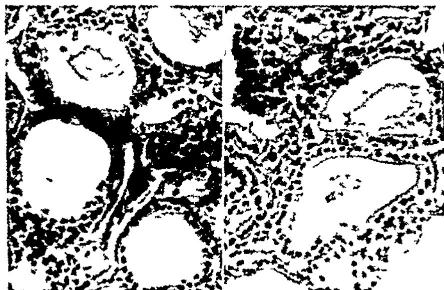


Fig 54 Photomicrographs x340 of thyroid of patient I D with Graves disease on the left at biopsy before thiouracil on the right at operation after thiouracil Note the increase in thyroid hypertrophy following thiouracil From Rawson R W et al Jour Clin Endocrinol 944 n 4

increased number and height of acinar cells extreme papillation and colloid depletion This picture of hyperplasia associated with depleted or absent thyroid hormone formation is due to stimulation by excessive thyrotrophin secretion from the anterior pituitary which has resulted from the low levels of circulating thyroid hormone in the blood Normally the thyroid gland is avid for thyrotrophin but the thiouracilized gland has an increased avidity for thyrotrophin These goitrogens have also been shown to augment thyrotrophin activity both in vitro and in the living organism (see Part III)

When iodine is administered simultaneously with thiourea derivatives goitrogenesis is not inhibited In toxic goiter, however the administration of the two drugs has a beneficial synergism in which the thiourea derivative inhibits hormone synthesis while the iodine penetrates the gland as inorganic iodine and promotes parenchymal involution, decrease in vascularity, and colloid storage (Figs 54-7)



Fig 55 Photomicrographs of thyroid of patient E K with Graves disease at operation after thiouracil on the left x170 on the right x43 Note the marked hyperplasia with papillary infoldings and scarcity of colloid From Rawson R W et al Jour Clin Endocrinol 1944 n 6

The inhibition of thyroid hormone formation by these compounds has been ascribed to an alteration in or interference with various enzyme systems which are essential for the formation of thyroid hormone Another hypothesis maintains that these compounds bind iodine so that it is unavailable to the thyroid cells

A large number of thiourea derivatives are available and have been used clinically It is therefore important to consider some of them individually so that the clinician may have a clear picture of their relative values in the treatment of toxic goiter The therapeutic aims sought with ideal medical treatment of thyrotoxicosis are (1) rapid and certain amelioration of the disease (2) permanent arrest of the hyperthyroidism (3) decrease in the goiter (4) recession, or at least no progression of

exophthalmos (5) minimal or no drug toxicity and (6) inexpensiveness and general availability of the chemotherapeutic agent These ideal requirements are met in part by many of the thiourea derivatives but as will be seen all fail significantly in several respects

Thiourea

This basic thiocarbonamide was the first antithyroidal agent tried in the treatment of toxic goiter It was quickly abandoned because of its

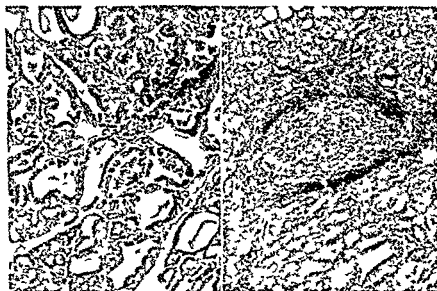


Fig 56 Photomicrograph x85 of the thyroid of patient b B with Graves disease on the left at biopsy before thiouracil on the right at operation after thiouracil Note the lymphoid hyperplasia in the post thiouracil specimen From Rawson R W et al J Clin Endocrinol 1944 p 5

unpleasant taste and odor as well as its marked toxicity McGavack[70] and Morgans [1] have emphasized its toxic effect on the bone marrow with the production of agranulocytosis However in the series of 118 patients treated with thiourea for long periods by Danowski and his colleagues no serious reactions were encountered except for cases of drug fever These authors consider it less toxic than thiouracil This is the largest series treated with thiourea but all of these cases received

iodine as well The ultimate cure rate in this group of patients was not determined since only 8 of the 118 patients were observed after thiourea withdrawal In these 8 patients therapy was maintained for 6 to 24 months and 5 of them appear to have had permanent remissions but relapses occurred even after two years of treatment

Kent, Shipley, and Rundell [3] have compared thiourea with propyl thiouracil in the treatment of thyrotoxicosis in a series of 100 cases They found thiourea effective in a range of dosage comparable to that of propylthiouracil namely 0 1 to 0 3 gm daily Toxic reactions were frequent, however, occurring in at least 16 per cent of all cases and



Fig 57 Thyroid gland in Graves disease case No 24684 Magnification = 1,0X A Before medication B After thiouracil C After thiouracil and iodine From Rawson R W et al Jour Clin Invest., 1945 xxiv 873

consisted of nausea fever dermatitis and arthritis The relapse rate after drug withdrawal in 27 cases treated for 3 months to years was 77 per cent Their data disclosed no correlation of relapse rate with age size of the gland duration of treatment severity of the disease or the type of gland These workers like Danowski administered iodides simultaneously with thiourea and propylthiouracil and noted no interference with the efficacy of the antithyroidal drug

Thiouracil Propylthiouracil and Methylthiouracil

These compounds may be considered as a group since they have received the widest use and have in the past been the drugs of choice

particularly propylthiouracil Thiouracil initially received wide application after it was first introduced by Astwood in 1943 [4] This compound is effective in alleviating most of the signs and symptoms of toxic goiter It will progressively lower the basal metabolism to euthyroid or hypothyroid levels and will concomitantly lower the protein bound iodine of the blood elevate the blood cholesterol and lessen excessive calcium excretion in the urine At the same time nervousness tremors and excessive perspiration will decrease Tachycardia will abate more slowly but eventually will disappear Thiouracil inhibits not only the hormone production of the hyperplastic gland of Graves disease but also the functioning metastases of thyroid cancer [5]

The effect of thiouracil upon the thyroid gland itself varies Occasionally there is striking and progressive increase in the gland size However many observers have found decreases in the size of the gland during thiouracil administration and a few have noted marked enlargement of the thyrotoxic gland similar to that produced in the thyroid gland of normal animals This increase in the size of the goiter may be prevented by the simultaneous administration of desiccated thyroid Thyroid enlargement caused by thiouracil may be an important consideration when the goiter is substernal or retrotracheal so that pressure symptoms ensue

Histologically thiouracil causes thyroid hyperplasia loss of colloid and increased vascularity in the already hyperplastic gland of thyrotoxicosis The normal human thyroid will not show hyperplasia following amounts of thiouracil administered in doses and for periods that cause striking changes in the thyrotoxic gland [7] Clinically as well the normal human subject is resistant to the induction of hypothyroidism by ordinary doses of thiouracil

In the treatment of toxic goiter the range of dosage for thiouracil has been from 0 4 to 0 8 gm daily given in 3 to 4 divided doses at regularly spaced intervals in order to maintain a constant level of antithyroidal effect As the basal metabolism approaches normal the dosage may be reduced and when euthyroidism is achieved a maintenance dose of 50 to 100 mg daily may be adequate If excessive dosage is maintained hypothyroidism of varying degree may ensue This state however is readily reversible with omission or reduction in the dosage of the compound

In toxic diffuse goiter the basal metabolism usually falls at the rate of 1 per cent for each day of treatment whereas in toxic nodular goiter the basal metabolism usually declines at the rate of 0 5 per cent daily [8]

iodine as well The ultimate cure rate in this group of patients was not determined since only 8 of the 118 patients were observed after thiourea withdrawal In these 8 patients therapy was maintained for 6 to 24 months and 5 of them appear to have had permanent remissions, but relapses occurred even after two years of treatment

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Fig 57 Thyroid gland in Graves disease case No 24684 Magnification = 170X A Before medication B After thiouracil C After thiouracil and iodine From Rawson R W et al Jour Clin Invest 1945 xxiv 875

consisted of nausea fever dermatitis and arthritis The relapse rate after drug withdrawal in 27 cases treated for 3 months to - years was 77 per cent Their data disclosed no correlation of relapse rate with age size of the gland duration of treatment severity of the disease, or the type of gland These workers like Danowski administered iodides simultaneously with thiourea and propylthiouracil and noted no interference with the efficacy of the antithyroidal drug

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These compounds may be considered as a group since they have received the widest use and have in the past been the drugs of choice,

ciated clinical phenomena and premonitory symptoms have not proved safe guides. Serious reactions have occurred at both high and low dosage levels, with short and with long treatment, and with both constant and intermittent administration of the drug.[31] In the early cases fatalities from agranulocytosis resulted in half of the affected patients, but the use of penicillin and other antibiotics in large doses has considerably reduced this fatality rate. Our own experience demonstrated that weekly observation of the leucocyte count would frequently show leucopenia developing under thiouracil therapy. In these circumstances the patient received closer supervision both clinically and hematologically. At times agranulocytosis was averted by prompt omission of the drug. Many patients with thyrotoxicosis have moderate leucopenia as part of the disease and this may render difficult the evaluation of depressions in the total white blood count or in the number of granulocytes occurring during the course of thiouracil administration. However, a persistent and increasing decline in the total white count and granulocytes must be taken as an indication of bone marrow depression by the drug and demands its omission or the closest supervision of the patient.

Drug Fever and Dermatitis

Drug fever and *dermatitis* are seen in 6 per cent of patients under treatment with thiouracil. These are allergic phenomena which disappear on omission of the compound. Drug fever usually appears during the second or third week of treatment and can be reproduced by readministration of the drug. Other types of skin reactions including purpura, maculopapular eruptions, urticaria and pruritis have occurred.

Swelling of the submaxillary or parotid glands, general adenopathy and *splenomegaly* may occur. *Liver damage* of slight to severe degree has been observed with fatalities from acute yellow atrophy.[7, 11] *Heart block, pericarditis, periarteritis nodosa, arthritis,* and *arthralgias* have all been reported in occasional instances.

In rats Purves and Griesbach[34] have produced carcinoma of the thyroid with pulmonary metastases. Bielschowsky[3] observed that allylthiourea potentiated the carcinogenic effect of acetylaminofluorene. Liver tumors have regularly been produced in rats fed thiourea for long periods.[36] Recently generalized parathyroid hyperplasia with hyperparathyroidism and osteitis fibrosa has been produced in rats maintained on thiourea, thiouracil or methylthiouracil.[37]

There are numerous exceptions to this general rate of response but it serves as a useful guide in either the pre operative or the continuous use of either thiouracil or propylthiouracil In instances of unquestioned thyrotoxicosis *failure to respond* adequately during the first eight weeks of treatment may be caused by previously administered iodine or an exceptionally large goiter It has been frequently observed that previous administration of iodine decelerates the response to thiouracil presumably by increasing the storage of hormone in the gland It should be stressed that pre iodinization slows but does not inhibit the characteristic response to thiouracil Simultaneous administration of thiouracil and iodine however, except in some patients with large goiters, usually produces a fall in basal metabolism at the same rate as thiouracil alone or for that matter as iodine alone The average initial decrease in basal metabolism with thiouracil is in fact closely parallel to that which occurs following the administration of iodine with the important difference that with thiouracil there is no leveling off at hypermetabolic levels but a steady decrease to normal or low metabolism values

On the other hand failure to respond to average doses of thiouracil may be an indication of lack of thyrotoxicosis or the need for increasing the amount of the drug Such cases need careful review from a diagnostic standpoint It is our opinion in this connection that thiouracil or its derivatives is not a suitable agent for use as a therapeutic test in the diagnosis of thyrotoxicosis because a given dose will not invariably ameliorate thyrotoxicosis as iodine will and also because *thiouracil may* be toxic

The usefulness of thiouracil or its derivatives as substitutes for thyroidectomy in the treatment of toxic goiter depends chiefly upon their ability to induce a lasting remission with minimal toxic effects *The toxicity of thiouracil* was evident even before there was a consensus on its ability to induce a sustained remission These toxic effects were various and involved numerous tissues and organs [illegible] but the most serious effects were upon the bone marrow with the production of agranulocytosis in about [illegible]5 per cent of all cases About 13 per cent of cases have shown adverse reactions to the drug [30]

Agranulocytosis

Agranulocytosis has occurred at all periods of treatment though it is most frequent between the fourth and eighth weeks of therapy Dosage duration of treatment constant or intermittent therapy, asso

reactions is still unsettled. When it is used pre-operatively an incidence of granulocytosis of 0.4 per cent should be anticipated during the 4 to 8 weeks necessary to induce euthyroidism. Close clinical and hematological supervision is therefore just as necessary in this group of patients as in the group that is treated for prolonged periods of time. Improvement in the treatment of agranulocytosis with antibiotics has greatly reduced the fatality rate from this serious complication but the incidence of leucopenia and agranulocytosis is high enough to indicate that propylthiouracil needs replacement by safer antithyroidal compounds.

Methylthiouracil has been used much less extensively than either thiouracil or propylthiouracil in the treatment of thyrotoxicosis. It has been used either in the preparation of patients for thyroidectomy or for prolonged periods for the induction of permanent remission of thyrotoxicosis. The effective dosage has been essentially like that of propylthiouracil, 00 to 400 mg daily in divided doses. Methylthiouracil has been used widely in Denmark and England where it was first introduced. As with thiouracil and propylthiouracil the bulk of the evidence indicates that previous iodinization, especially when prolonged, retards the rate of response to methylthiouracil.

Toxic reactions to methylthiouracil have been fairly numerous. Barfred,[4] for example, reported an incidence of 78 per cent of toxic reactions in a group of patients receiving 1 2 gm daily but only 47 per cent in the group receiving less than 570 mg daily. His entire series numbered 68 patients with one case of agranulocytosis. Other toxic reactions included fever, dermatitis, increased urobilinuria, and one case of central nervous system disturbance of obscure nature. Other authors including Frisk,[13] Meulengracht,[14] and McCullagh,[4] have found a toxic reaction rate varying from 5 to 1 per cent in relatively small series of cases. Drug fever, dermatitis, arthralgias, leukopenia, and agranulocytosis are the chief complications so far reported, and their incidence indicates clearly that methylthiouracil is much more toxic that propylthiouracil. In view of this experience methylthiouracil offers no advantage over propylthiouracil and in fact increases the hazard to the patient.

The therapeutic value of the antithyroidal compounds depends upon their ability to induce permanent remission of thyrotoxicosis with minimal toxic effects. The relative toxicity of three of the most widely used compounds has been considered. The least toxic of these drugs, propylthiouracil, is comparable in morbidity and mortality with thyroidectomy in competent hands. One may therefore properly consider next the expectancy of *cure or permanent remission* when thiourea derivatives

As clinical and experimental evidence of thiouracil toxicity accumulated, related compounds of equivalent potency were studied and several were found to have strikingly less toxicity, particularly propylthiouracil (6-N-propylthiouracil). *Thiouracil has therefore been abandoned as a therapeutic agent* in the treatment of thyrotoxicosis and has been supplanted by propylthiouracil and to a lesser extent by methylthiouracil (4-methyl-2-thiouracil).

Propylthiouracil has had extensive clinical trial since 1946 in several thousand cases. The initially recommended dose of 75 to 100 mg daily[-38] was found inadequate for most patients and eventually a daily dose of 200 to 400 mg administered in 3 or 4 divided doses was established as the effective dose in over 90 per cent of patients. The rate of decrease in the basal metabolism varies considerably, ranging from 0.5 to 5 per cent daily. If the clinical and metabolic status of the patient does not improve after several weeks of therapy, the daily dose may be increased by 50 or 100 mg. An occasional patient will not completely respond to as much as 600 mg daily.

Propylthiouracil, like thiouracil, has been utilized in three ways in the treatment of toxic goiter: (1) as the chief therapeutic agent for the continuous suppression of thyrotoxicosis until complete remission is secured; (2) in the pre-operative preparation of patients for thyroidectomy, usually in combination with iodides, and (3) as a synergist with iodides for the control of thyrotoxicosis until permanent remission occurs.

Early reports of negligible *toxicity from propylthiouracil* have not been substantiated by longer and more extensive experience with this compound, though it is clearly less toxic than thiouracil. In our experience the spectrum of toxic reactions has been narrower than that of thiouracil but has included 2 cases of agranulocytosis, 1 case of parotitis, 2 cases of drug fever and several cases of dermatitis. Bartels[8] reporting the experience of the Lahey Clinic in 820 cases found toxic reactions in 1.8 per cent, with an occurrence of agranulocytosis in 0.4 per cent of the cases. Other toxic reactions consisted of leucopenia, fever and dermatitis. There were no deaths. These figures from the Lahey Clinic must be regarded as minimal for the incidence of toxic reactions because the drug was given for relatively short periods of time during the preparation of patients for thyroidectomy.

Other investigators[39, 40, 41] have reported arthralgias and toxic hepatitis. Several deaths from agranulocytosis have occurred. As with thiouracil, agranulocytosis or severe leucopenia may occur after many months of administration of propylthiouracil, the true incidence of toxic

reactions is still unsettled When it is used pre operatively an incidence of granulocytosis of 0 4 per cent should be anticipated during the 4 to 8 weeks necessary to induce euthyroidism Close clinical and hematological supervision is therefore just as necessary in this group of patients as in the group that is treated for prolonged periods of time Improvement in the treatment of agranulocytosis with antibiotics has greatly reduced the fatality rate from this serious complication but the incidence of leucopenia and agranulocytosis is high enough to indicate that propylthiouracil needs replacement by safer antithyroidal compounds

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are used as the sole method of treatment in toxic goiter Here again thiouracil, propylthiouracil and methylthiouracil are the compounds with most adequately reported experience

Many theoretical factors enter into the production of permanent remissions with the thiouracils The duration of treatment is a prime factor other important factors are the severity of the disease and the size of the goiter The duration of the disease before treatment appears not to be significant and the same applies to the ages of the patient

There is no consensus on the duration of therapy but all agree that 6 months is the probably minimum period necessary to produce permanent remission Williams[46] however, considers 10 to 15 months as the optimal period of treatment, although some of his patients were under continuous therapy for more than 2 years His most persistent remissions occurred in female patients with small goiters and mild thyrotoxicosis In his series of 119 cases 57 patients or 48 per cent had remissions lasting 1½ to 4½ years In 51 patients, or 42 per cent remissions lasted over 2 years Williams emphasizes that the most significant part of the treatment with the thiouracils is the prolonged maintenance of a euthyroid state In other words prolonged therapy with incomplete control of the hyperthyroidism will not induce either temporary or permanent remission

Bartels[47] treated 21 patients with thiouracil and was able to induce prolonged remission in 8, or 38 per cent These patients were observed for an average period of 13 months following the omission of therapy Barr,[48] in a series of 89 patients found a permanent remission rate between 40 and 50 per cent in those followed for 2 years after omission of the thiouracils This is in close agreement with Williams[46] McGavack[50] has reported permanent remissions in 29 of 43 patients followed for periods of 18 to 37 months after the omission of thiouracil This represents a remission rate of 67 4 per cent one of the highest reported On the other hand Starr and his associates[49] studied the remission rate following the use of propylthiouracil, utilizing the serum protein bound iodine as the index of thyroid function Forty patients were treated for periods ranging from 4 to 15 months with dosages varying from 150 to 600 mg daily In one fourth of the patients the disease was not controlled with usual or even high daily doses over periods from [illegible] to 15 months The protein bound iodine remained elevated and clinical thyrotoxicosis persisted The daily amount of propylthiouracil required to maintain normal or low concentrations of protein-bound iodine varied considerably from patient to patient Maintenance of euthyroidism for 10 months

was not followed by a single instance of permanent remission upon omission of the drug

The incidence of permanent remissions following the use of methyl thiouracil has been reported by Frisk [41] and Meulengracht [44] Frisk found a remission of at least 18 months in 14 per cent or 18 of 1 6 patients treated for prolonged periods Meulengracht treated 170 patients —the majority for a period of 1. months some for as little as 5 months and a few up to 37 months The observation period after the termination of treatment varied from 3 to 34 months with an average of 17 months Unfortunately basal metabolism tests were not done in most instances the clinical state serving as the only guide to the level of thyroid function He observed a relapse rate of 9 per cent after omission of treatment for 3 months but felt that more would appear as time passed In those patients who did have basal metabolism tests values up to plus o per cent were apparently considered within the normal range by this author

Starr [49] has summarized his feelings about the use of the thiouracils as follows If a medication will induce a prolonged if not permanent cure of hyperthyroidism in 85 per cent of patients even though a year s treatment is involved general use of the drug for this purpose is warranted in spite of the possibility of some drug intoxication If on the other hand only one third or fewer of the patients receive lasting benefit it would seem that use of the drug in prolonged therapy is unwarranted We are in substantial agreement with this point of view but feel that the thiouracils will not establish themselves as the sole therapeutic agents in the treatment of toxic goiter unless there results permanent rather than prolonged cure in the vast majority of patients This is clearly not yet true of the antithyroidal goitrogens that have been adequately investigated to the present time When one balances the actual and potential toxicity of these compounds against the permanent remission rate and also throws into the balance the necessarily prolonged period of close observation and treatment it is our opinion that the thiouracils have failed to meet the minimal requirements for the satisfactory treatment of toxic goiter

Astwood and his associates [4] in an analysis of the therapeutic results obtained in 101 patients with hyperthyroidism observed for four years after the termination of antithyroid drug therapy report that 23 7 per cent had a relapse within 3 months o 8 per cent had recurrences from 3 to 48 months later and 55 5 per cent remained euthyroid Second and third courses of treatment yielded lower remission rates than the first but increased the total number of persons with prolonged remission to 70 3

per cent of the total series The frequency of recurrences decreased gradually as the duration of remission increased Only a decrease in goiter size during treatment was found to improve the ultimate result significantly Astwood concludes that patients with primary hyperthyroidism and a small diffuse goiter are most likely to have a prolonged remission

While the thiouracils have not established themselves as the best method of attaining permanent remission or cure in most cases of toxic goiter, there is considerable agreement concerning their effectiveness in the *preparation of severely toxic patients for thyroidectomy* Their use in the preparation of patients with mild or moderate degrees of thyrotoxicosis for thyroidectomy has not become a standard procedure although in some clinics it is used routinely in all cases Moore and his associates [0] noted that thiouracil was better than iodine as a preparative for thyroidectomy, since it will regularly bring the patient to operation in a euthyroid state They also found somewhat less post operative fever and tachycardia in this group Technical difficulties however were increased since thiouracil accentuated the existent hyperplasia increasing vascularity and friability of the gland

Bartels [8] reviewing the large experience of the Lahey Clinic considers that the thiouracils should be routinely used in all thyrotoxic patients before thyroidectomy The drug is administered until euthyroid levels are attained with particular care to avoid hypothyroidism and its associated morphine sensitivity Three weeks before the operation iodide is added so that the gland will become involuted less vascular, and less friable With this program an operative mortality of less than 0.1 per cent has been achieved in a series of 1,40 cases No deaths occurred from the drug itself although there were several serious reactions

Pemberton Haines and Keating [1] describing the experience of the Mayo Clinic in a series of comparable size, found that the thiouracils were rarely necessary in pre-operative management, except in severely toxic patients amounting to about 5 per cent of the whole group They utilized iodine alone for an average period of 2 weeks and experienced an over-all mortality of 0.18 per cent The mortality occurred entirely in the patients with toxic nodular goiter who were for the most part in the older age groups

In our own experience with the severely toxic patient propylthiouracil with the subsequent addition of iodine has proved a certain method of attaining euthyroidism and a relatively involuted gland before thyroidectomy In this group of patients operation is no longer hazardous and

needs no multiple procedures For the mildly toxic patient preparation with iodine alone is ordinarily adequate is certainly speedier and avoids the risks of toxic drug reactions In the group of moderate toxicity it is our opinion that propylthiouracil followed by iodine is an ideal preparative method provided the patient is carefully observed for the occurrence of toxic drug reactions In patients of moderate or severe toxicity who have received iodine alone without achieving complete control of the thyrotoxicosis propylthiouracil should be added until euthyroidism is reached *The omission of iodine in these patients is hazardous since it may precipitate a thyroid crisis* thus it should be continued along with the propylthiouracil until thyroidectomy This may involve many weeks or even months of combined therapy but the time spent in thus preparing the patient will ensure minimal or no mortality and morbidity

Other Antithyroidal Goitrogens Many antithyroidal goitrogens have been tested clinically in the treatment of toxic goiter but have been discarded because of adverse reactions [1] still others are now the subject of active clinical experimentation Thiobarbital and aminothiazole have proved excessively toxic Both have caused hepatitis agranulocytosis drug fever and dermatitis with several fatalities in small series [3 4] Stanley and Astwood in man and McGinty and Wilson in monkeys [6] have assayed a wide range of newly synthesized antithyroidal goitrogens and have found 2 mercapto imidazole about 20 times as potent as thiouracil and 1 methyl 2 mercapto imidazole about 100 times more potent than thiouracil The last named compound known under the generic name of methimazole (tapazole) has received fairly extensive clinical use It is employed in a daily dosage of 15 to 45 mg and utilized under the same conditions and in the same way as other thiouracils Its toxic qualities appear similar in kind and degree to those of propylthiouracil

Iodinated thiouracils have been tested clinically by Williams and his co workers [7] They theorized that iodination of thiouracil might concentrate the latter compound in the thyroid because of the avidity of the thyroid for iodine The response of the patients to these compounds however was similar to that following iodide therapy rather than that produced by thiouracil

THYROIDECTOMY IN THE TREATMENT OF TOXIC GOITER

The treatment of toxic goiter with antithyroidal compounds whether iodides or the thiouracils leads to chemical alterations within the gland

per cent of the total series. The frequency of recurrences decreased gradually as the duration of remission increased. Only a decrease in goiter size during treatment was found to improve the ultimate result significantly. Astwood concludes that patients with 'primary' hyperthyroidism and a small diffuse goiter are most likely to have a prolonged remission.

While the thiouracils have not established themselves as the best method of attaining permanent remission or cure in most cases of toxic goiter, there is considerable agreement concerning their effectiveness in the *preparation of severely toxic patients for thyroidectomy*. Their use in the preparation of patients with mild or moderate degrees of thyrotoxicosis for thyroidectomy has not become a standard procedure, although in some clinics it is used routinely in all cases. Moore and his associates [0] noted that thiouracil was better than iodine as a preparative for thyroidectomy, since it will regularly bring the patient to operation in a euthyroid state. They also found somewhat less post operative fever and tachycardia in this group. Technical difficulties, however, were increased, since thiouracil accentuated the existent hyperplasia, increasing vascularity and friability of the gland.

Bartels [8] reviewing the large experience of the Lahey Clinic considers that the thiouracils should be routinely used in all thyrotoxic patients before thyroidectomy. The drug is administered until euthyroid levels are attained, with particular care to avoid hypothyroidism and its associated morphine sensitivity. Three weeks before the operation iodide is added so that the gland will become involuted, less vascular, and less friable. With this program an operative mortality of less than 0.1 per cent has been achieved in a series of 1,240 cases. No deaths occurred from the drug itself, although there were several serious reactions.

Pemberton, Haines and Keating [1] describing the experience of the Mayo Clinic in a series of comparable size, found that the thiouracils were rarely necessary in pre-operative management except in severely toxic patients amounting to about 5 per cent of the whole group. They utilized iodine alone for an average period of 2 weeks and experienced an over all mortality of 0.18 per cent. The mortality occurred entirely in the patients with toxic nodular goiter who were for the most part in the older age groups.

In our own experience with the severely toxic patient propylthiouracil with the subsequent addition of iodine has proved a certain method of attaining euthyroidism and a relatively involuted gland before thyroidectomy. In this group of patients operation is no longer hazardous and

short of total removal of the normal gland will produce myxedema because even the smallest remnants will quickly regrow to supply the normal requirements for thyroid hormone. On the other hand a generous subtotal resection of the hyperplastic gland will ordinarily result in sufficient hypofunction of the remaining tissue to produce permanent euthyroidism. In 3 of 6 cases that came to autopsy several years after subtotal thyroidectomy for toxic goiter Pemberton [61] found areas of cellular hyperplasia in the thyroid remnants; the other 3 cases had none. *The physiological and pathological behavior of thyroid* remnants after subtotal thyroidectomy is receiving new attention since the introduction of radioactive iodine in the study of thyroid function. Freedberg [149] has found in some of our patients who were clinically and metabolically euthyroid normal iodine avidity in remaining thyroid tissue months to years after bilateral subtotal thyroidectomy for Graves' disease. He encountered, however, slightly elevated I^{131} uptakes persisting in thyrotoxic patients who had been rendered euthyroid by radioactive iodine.

The results of total thyroidectomy in the treatment of toxic goiter have been reported by Scott and Ramey following its use in 280 patients.[377] Post-operative myxedema was an inevitable consequence requiring a lifetime of treatment with desiccated thyroid; however, persistent or recurrent hyperthyroidism was completely eliminated. In the hands of these surgeons the operative mortality and the incidence of surgical complications compare favorably with the incidence in subtotal thyroidectomy, except that bilateral recurrent laryngeal nerve injury occurred more frequently than with subtotal thyroidectomy.

The evaluation of subtotal thyroidectomy as a therapeutic procedure depends upon the incidence of permanent remission as compared with the inherent mortality and complications. This evaluation must therefore deal with the following conditions: (1) operative mortality, (2) persistent and recurrent thyrotoxicosis, (3) injury to the recurrent laryngeal nerves, (4) hypoparathyroidism, (5) hemorrhage, (6) respiratory obstruction, (7) thyrotoxic crisis, (8) progressive exophthalmos and (9) myxedema.

While the *mortality from thyroidectomy* for toxic goiter has been reduced to minimal figures, it still varies considerably in accordance with the skill and experience of the surgeon. Pemberton [51] has recently reported thyroidectomy without any mortality in 611 consecutive cases of exophthalmic goiter and a mortality of 0.4 per cent in 496 cases of toxic nodular goiter. Since he had no deaths in 1131 cases of non-toxic

itself but leaves intact the total gland structure These compounds are effective through an alteration in iodide metabolism and hormone storage synthesis or delivery Thyroidectomy on the other hand affects the disease by extirpation of the gland either in part or totally

Excision of thyroid tissue for toxic goiter has been practiced since 1880 when it was first utilized by the French surgeon Tillaux in a case of exophthalmic goiter Extensive resections were advocated by Dunhill in 1908 but the modern operation of bilateral subtotal thyroidectomy was introduced and perfected by Halsted Total thyroidectomy for the treatment of toxic goiter was advocated by Gilman and Kay in 1928 and was reintroduced by Scott in 1939 The mortality associated with thyroidectomy was strikingly reduced by the preoperative use of iodides Multiple stage operations have been abandoned since the combined use of the thiouracils and iodides have made it possible to achieve euthyroidism before thyroidectomy in severely toxic patients The mortality from surgery has undoubtedly reached minimal figures but the complications of thyroidectomy require serious consideration when it is advocated for the treatment of Graves disease

The type of operation most often utilized in the treatment of toxic goiter is bilateral subtotal thyroidectomy This operation is standardized from a technical standpoint although minor deviations from the conventional technique are resorted to by individual surgeons to avoid injury to the recurrent laryngeal nerves or trauma to the parathyroids Deciding on the exact amount of tissue to remove at operation is far from a quantitative procedure since it depends upon the surgeon s judgment experience and skill There is a relationship between the amount of tissue removed and the attainment of euthyroidism for hemithyroidectomy rarely causes permanent remission of hyperthyroidism whereas total thyroidectomy invariably substitutes myxedema for thyrotoxicosis Moreover many feel that maximal subtotal thyroidectomy will more regularly result in euthyroidism or myxedema than will less extensive resections Cattell and Morgan [63] for example, assert that the extent of the thyroidectomy will directly influence the incidence of post operative myxedema or persistent thyrotoxicosis Crile on the other hand states that the development of post operative hypothyroidism is not closely correlated with the amount of tissue resected

An important difference exists however between the normal gland and the thyrotoxic gland Subtotal removal of the normal gland will not cause hypofunction of the remnants and resultant myxedema Extensive experience at the Beth Israel Hospital has demonstrated that nothing

short of total removal of the normal gland will produce myxedema because even the smallest remnants will quickly regrow to supply the normal requirements *for thyroid hormone.* On the other hand a generous subtotal resection of the hyperplastic gland will ordinarily result in sufficient hypofunction of the remaining tissue to produce permanent euthyroidism. In 3 of 6 cases that came to autopsy several years after subtotal thyroidectomy for toxic goiter Pemberton found areas of cellular hyperplasia in the thyriod remnants; the other 3 cases had none. The physiological and pathological behavior of thyroid remnants after subtotal thyroidectomy is receiving new attention since the introduction of radioactive iodine in the study of thyroid function. Freedberg has found *in some of our patients* who were clinically *and* metabolically euthyroid normal iodine avidity in remaining thyroid tissue *months to years after bilateral subtotal thyroidectomy for Graves* disease. He encountered however slightly elevated I^{131} uptakes persisting in thyrotoxic patients who had been rendered euthyroid by radioactive iodine.

The results of total thyroidectomy in the treatment of toxic goiter have been reported by Scott and Ramey following its use in 260 patients.[47] Post operative myxedema was an inevitable consequence requiring a lifetime of treatment with desiccated thyroid; however persistent or recurrent hyperthyroidism was completely eliminated. In the hands of these surgeons the operative mortality and the incidence of surgical complications compare favorably with the incidence in subtotal thyroidectomy, *except that bilateral recurrent laryngeal nerve injury* occurred more frequently than with subtotal thyroidectomy.

The evaluation of *subtotal thyroidectomy* as a therapeutic procedure depends upon the incidence of permanent remission as compared with the inherent mortality and complications. This evaluation must therefore deal with the following conditions: (1) operative mortality, (2) persistent and recurrent thyrotoxicosis, (3) injury to the recurrent laryngeal nerves, (4) hypoparathyroidism, (5) hemorrhage, (6) respiratory obstruction, (7) thyrotoxic crisis, (8) progressive exophthalmos, and (9) myxedema.

While the *mortality from thyroidectomy* for toxic goiter has been reduced to minimal figures it still varies considerably in accordance with the skill and experience of the surgeon. Pemberton[11] has recently *reported thyroidectomy without any mortality in 611 consecutive cases* of exophthalmic goiter and a mortality of 0.4 per cent in 496 cases of *toxic nodular goiter.* Since he had no deaths in 1131 cases of non toxic

nodular goiter it is evident that patients with toxic nodular goiter were the only ones with a serious surgical risk. The patients in this group are likely to be older and therefore more susceptible to mortality from the combined effects of thyrotoxicosis and cardiovascular disease.

Similarly, Cattell [68] has reported a mortality of 0.24 per cent in a recent series of 1630 patients subjected to thyroidectomy for hyperthyroidism at the Lahey Clinic. In this series 2 of the 4 deaths were due to cardiovascular complications and the other 2 were caused by tracheal obstruction. Ravdin [69] encountered a mortality of 0.9 per cent in 655 thyrotoxic patients thyroidectomized in the 10 year period 1937-47. Of his 6 deaths 2 were due to cardiovascular complications, 1 to thyrotoxic crisis, 1 to septicemia, and 2 to cardiac arrest of unexplained origin. Crile [64] in a recent series of thyroidectomies for toxic goiter equally divided between diffuse and nodular had no mortality in 315 cases. Bertelsen [70] had 7 deaths in 910 thyroidectomies for thyrotoxicosis during the 5-year period 1940-45, a mortality rate of 0.77 per cent. In 4 instances death was due to thyrotoxic crisis, in 2 to cardiovascular complications, and in 1 to bronchopneumonia. In the same paper he presents a more recent series comprising 164 operations, most of them for toxic diffuse goiter, with no mortality. Goldman [71] has reported a mortality rate of 1.0 per cent in 379 operations for toxic diffuse goiter and 0.5 per cent in 179 operations for toxic nodular goiter. Most of these operations were performed by the resident staff of the hospital.

From the preceding data it may be inferred that teaching clinics will have a significantly higher operative mortality than obtains in those clinics where thyroidectomy is performed entirely by experienced surgeons.

Persistent thyrotoxicosis following thyroidectomy represents failure to cure the disease and necessitates in almost every instance further treatment by non-surgical methods or by an additional thyroidectomy. The incidence of persistent thyrotoxicosis is consequently of importance in the evaluation of surgical treatment.

Persistent thyrotoxicosis requires definition and separation from *recurrent thyrotoxicosis*. Its definition varies considerably in the literature but in our opinion it may be described as a state of thyroid hyperfunction which remains after thyroidectomy of any degree and which manifests itself usually in milder form within days, weeks or months following operation. Recurrent thyrotoxicosis represents reappearance of hyperthyroidism after an interval of euthyroidism or even hypothyroidism lasting long enough to make it improbable that the original attack had

persisted in *mild form following the thyroidectomy* The distinction between persistence and recurrence is important since the former represents failure in whole or in part of the therapeutic procedure whereas the latter is a new episode of thyrotoxicosis which cannot fairly be ascribed to failure of the original method of treatment

The exact incidence of persistent thyrotoxicosis is not known because of lack of careful clinical and laboratory studies in an adequate number of patients In our own clinic where persistence and recurrence are differentiated 35 patients with toxic goiter treated by radical subtotal thyroidectomy between 193- and 1936 showed persistent thyrotoxicosis in 3 per cent and recurrent hyperthyroidism in 1 per cent[18] Crile has found a persistence rate of 1 7 per cent and a recurrence rate of 6 9 per cent in a series of 117 cases subjected to thyroidectomy by the con*ventional technique*[14] *The same author however in a comparable series* has found a recurrence rate of but 1 per cent when he utilized his *anatomical technique for thyroidectomy He does not differentiate* residual from recurrent hyperthyroidism in this latter group Thompson Morris and Thompson[7] surveying the results of thyroidectomy in 190 cases reported in 1930 found persistence in 18 5 per cent and recurrence in 1 per cent This high rate of persistence was very likely due to inadequate subtotal thyroidectomy

The chief difficulty that confronts the clinical investigator in attempting to separate persistent from recurrent thyrotoxicosis is the striking amelioration of the disease produced by even minimal subtotal thyroidectomy Unless the post operative state is scrutinized critically the euphoria weight gain and lessened thyrotoxicosis of the patient readily obscure the persistent state

Data on the incidence of recurrent thyrotoxicosis are abundant and represent adequate follow up studies in large series of cases One may fairly argue that the over all recurrence rate will reveal the effectiveness of thyroidectomy since it will inevitably include both true recurrences and those cases that had not finally attained euthyroidism as a result of the initial *operation From 1930 through 1947 the recurrence rate has been* reported in over 26 000 thyroidectomized patients by 3 authors[71] In *this large series the incidence of recurrence ranged from -* per cent to 7 9 per cent The highest rate of recurrence occurred before 1940 Since then recurrence rates of less than 10 per cent have been the rule Current experience indicates an even lower incidence of recurrent thyrotoxicosis *following* subtotal thyroidectomy The rate of recurrence has been 4 per cent in Cattell s series of 381 patients[7] - 3 per cent in

Ravdin's series of 655 patients [69], 2 1 per cent in 144 patients operated by Crile with his 'anatomic' technique and 6 8 per cent in 117 cases operated by him with the conventional technique [964], 3 6 per cent in Goldman's series of 379 patients with toxic diffuse goiter, and 0 5 per cent in his 179 patients with toxic nodular goiter Bertelsen [70] has approached the problem of recurrence uniquely by investigating the incidence of recurrence in thyrotoxic patients admitted to the medical out-patient department of the Rigshospital in Copenhagen Of 398 patients with toxic diffuse goiter, 5 65 per cent represented recurrences, of 249 patients with toxic nodular goiter 2 8 per cent were recurrences All these recurrences followed either one or more subtotal thyroidectomies Bertelsen's figures as well as Goldman's [71] indicate that subtotal thyroidectomy is less often followed by recurrence when employed in the treatment of toxic nodular goiter than when used in the treatment of toxic diffuse goiter

The treatment of persistent and recurrent thyrotoxicosis is significantly complicated by the factor of precedent thyroidectomy, since further surgery in the thyroid gland entails a higher mortality rate and a greater incidence of injury to the recurrent laryngeal nerves and the parathyroid glands For this reason thyroidectomy has not been utilized and in our opinion should not be utilized for the treatment of persistence and recurrence This group of cases may be controlled by the prolonged administration of stable iodides, particularly if the thyrotoxicosis is mild The same considerations that apply to the use of iodides in the initial therapy of thyrotoxicosis obtain in the persistent and recurrent group namely that iodides will frequently convert mild thyrotoxicosis to euthyroidism but will serve only to lessen the toxicity of the moderate or severely hyperthyroid patient However since most patients with persistent thyrotoxicosis are but mildly toxic, iodides are a preferred treatment

In recurrent hyperthyroidism one should consider the degree of thyrotoxicosis the amount of glandular regrowth, and the presence of vocal cord palsy from the preceding thyroidectomy Here, too iodides serve well *in the mild cases and occasionally in the moderately* toxic group Propylthiouracil and iodides have a useful place in the treatment of persistent and recurrent thyrotoxicosis when iodides alone are unable to effect complete control Radioactive iodine is particularly effective in this entire group since it can achieve euthyroidism in all cases, however, dosage calculations may be difficult because of inability to assess thyroid gland size with accuracy Repeated thyroidectomy has been performed in about one half of the recurrent cases Bilateral thyroidectomy is quite

hazardous in patients with unilateral vocal cord paralysis as a result of the initial operation

Patients in whom recurrent hyperthyroidism is associated with marked regrowth of thyroid tissue usually require thyroidectomy although we have had excellent results in this group of patients with radioactive iodine therapy This treatment has induced euthyroidism and marked reduction in the size of the regrown tissue In these patients the control of the thyrotoxicosis may be secured by iodides or iodides combined with the thiouracils but the regenerated tissue may cause pressure symptoms or be the nidus of malignancy They should therefore be viewed as a special problem [9, 15]

Injuries to the Recurrent Laryngeal Nerves

The close anatomical relationship of the recurrent laryngeal nerves to the thyroid gland predisposes them to injury during thyroidectomy With injury to these nerves the vocal cords may become fixed in such a position as to interfere with respiration and phonation This interference is of major consequence when respiratory distress ensues requiring tracheotomy to save life it may so weaken or alter the speaking or singing voice as to deprive speakers or singers of their occupation or on the other hand it may produce such trivial changes in voice and respiration as to pass unnoticed

Injuries to the recurrent laryngeal nerves from subtotal thyroidectomy may be unilateral or bilateral complete or incomplete temporary or permanent The injury is caused by excessive traction crushing cutting or adventitious suturing of the nerve as it courses through or near the thyroid gland Occasionally hemorrhage into the nerve area may also produce damage Nerve injury during thyroidectomy ordinarily causes the vocal cord on the injured side to swing to the midline and to lose all or part of its mobility and tension Freedman [3] in his observations of nerve injury during total thyroidectomy found that the paralyzed cords were usually in the median line the position of abductor paralysis and that the paramedian or cadaveric position was rare in recent paralyses In 45 total thyroidectomies of normal glands for the treatment of heart disease there occurred 10 instances or . per cent of cord paralyses Nine of these (o per cent) were unilateral and one (2 per cent) was temporarily bilateral Nine or 20 per cent were complete with a median line position of the affected cord and one or . per cent was partial In

only 3 cases was the damage permanent an incidence of 6 7 per cent The difficulty in avoiding nerve damage when removing the normal thyroid gland is emphasized by Scott s figures for nerve paralysis resulting from total removal of the hyperplastic gland of Graves disease In 56 operations there were 13 instances of nerve injury, 5 1 per cent There were 9 or 3 5 per cent unilateral and transient 2, or 0 8 per cent unilateral and permanent, and 2 or 0 8 per cent bilateral and permanent The permanent injuries in this series occurred in the first 47 operations and none occurred in the last 209 operations

The estimation of the true incidence of nerve injury from subtotal thyroidectomy requires examination of the cords before and after operation and cannot be determined by voice changes or the development of stridor Voice changes are likely to occur with cord paralysis but are not constant depending greatly on the position and tension of the involved cord Stridor or asthmatic breathing almost always occurs following bilateral injury but may be absent if the cords are not fixed in an abducted position, in these circumstances breathing is not difficult but loss of voice is common With unilateral paralysis the strength of the voice is lost and pitch is distinctly lowered so that a weak low pitched voice is characteristic Return of a normal voice occurs if the paralysis clears but a reasonably normal voice may also return after fixation of the injured cord when the normal cord moves beyond the midline to meet it and narrows the glottic aperture to that point essential for production of good tone Adequate volume of voice does not return with permanent unilateral paralysis When bilateral paralysis occurs the cords usually move to the midline in the position of abductor paralysis Initially there may or may not be aphonia depending upon the tonicity and degree of approximation of the cord eventually the voice returns As the cords approximate the glottis becomes an increasingly narrow chink so that inspiratory stridor develops requiring tracheotomy to provide adequate respiratory exchange There may be expiratory difficulty also, with the development of wheezing and simulation of bronchial asthma Bilateral *cord paralysis usually requires tracheotomy, and if the* paralysis is permanent the patient may need a permanent tracheotomy with a valved tube which allows air to enter through the tracheotomy opening during inspiration and to pass through the vocal cords on expiration permitting adequate phonation There are several operations for rehabilitation of the damaged cord which depend upon widening the gap between the cords according to the method of King [74] Kelly [illegible] or Woodman [illegible]

The incidence of cord paralysis varies considerably, depending upon

the skill of the surgeon the degree of thyroidectomy and possibly other factors such as the type of operation and the identification of the nerves at operation Most reports stress the incidence of permanent paralysis glossing over the occurrence of temporary nerve injury as of no significance However since temporary nerve injury may necessitate tracheotomy or may interfere for a period of months with occupations *depending upon an adequate speaking or singing voice its occurrence* should not be underemphasized In recent reports the incidence of this *complication of thyroidectomy has varied widely* Thus Ravdin [4] *has* reported 3 05 per cent temporary nerve injuries and 0 45 per cent *permanent damage with no bilateral injuries* Cattell [54] *incurred an* incidence of permanent unilateral injury of 1 per cent but gives no *figures for transient paralyses* Goldman [1] *reporting from a teaching* clinic had a total incidence of cord paralysis of 6 per cent for toxic *diffuse goiter and of 7 1 per cent for toxic nodular goiter* about half the cases in each group representing partial paralysis This author does not *state how many of these injuries were permanent* Bertelsen [70] *had 66* cases of cord paralysis in 910 operations for toxic goiter—an incidence of 7 5 per cent *of which* 0 per cent *were bilateral but temporary* Permanent injury occurred in per cent of his cases

Methods for the prevention of injury to the recurrent laryngeal nerves during thyroidectomy have been proposed by many The standard *subtotal thyroidectomy leaves a shelf of thyroid tissue posteriorly to* protect the nerves when in their usual location The results from this *general prophylactic approach have not however been completely satis* factory Lahey [71] in an effort to reduce further the incidence of this *complication suggested complete exposure of the nerves as a routine* procedure in thyroidectomy and he was thus able to decrease the *incidence of nerve injury by two thirds* Ravdin *with a similar experi* ence does not expose the nerves in every thyroidectomy He properly *points out that exposure alone will not prevent injury unless great care* is exercised throughout the operation to avoid blind application of *hemostats or careless suturing in the tracheo thyroid space* Our own experience has taught us that reliance on exposure of the nerve will not *prevent nerve injury unless it is associated with meticulous care to avoid* traction section crushing or suturing of the nerve Crile [84] has found *that extracapsular ligation of the inferior thyroid artery combined with* visualization of the recurrent nerve has greatly reduced his incidence of nerve injury Cope [4] also believes *that exposure of the nerve combined* with painstaking operative technique will prevent nerve injury Bertel

sen's incidence of permanent nerve injury is no higher than that of the most experienced thyroid surgeons although he rarely dissects the nerve free but relies instead upon a careful technique He performs his thyroidectomies under local anesthesia employing laryngoscopy during the operation If paralysis of the vocal cord is observed he exposes the recurrent nerve involved and in two cases has performed a successful neurolysis upon finding the nerve caught in a ligature[70]

All are agreed that secondary thyroidectomies are associated with an incidence of nerve injury of 10 to 15 per cent This is a minimal figure of the experienced operator and indicates that secondary thyroidectomy presents a considerable hazard to the nerves If a bilateral operation must be done bilateral nerve injury can be avoided through the employment of laryngoscopy after the resection of one side as originally practiced by Freedman[73]

Injury to the Parathyroid Glands

Bilateral subtotal thyroidectomy may cause injury to the parathyroids or be associated with the inadvertent removal of one or all of the four glands As a result there may occur varying degrees of hypoparathyroidism which may be latent temporary, or permanent The parathyroid glands are usually in close anatomical relationship to the thyroid gland so that removal of one or more is not unusual Crile[64] for example states that about half of his cases of tetany were due to resection of the parathyroids and that the other half were presumably due to hemorrhage or ischemia affecting the parathyroids Experience with identification of these glands in autopsy material is helpful, if not indeed essential for the avoidance of their removal during thyroidectomy Cattell[78] justifiably believes that at least two of the glands should be identified at operation Ravdin[79] as well as Lahey[83] advocate immediate reimplantation of suspected parathyroid tissue inadvertently removed

The determination of the incidence of post-operative hypoparathyroidism depends upon clinical observation and the estimation of the serum calcium concentration Symptoms and signs of parathyroid deficiency are due to increased neuromuscular excitability resulting from the low level of calcium ions in the blood and tissue fluids and will ordinarily appear in 1 to 5 days after operation The manifestations may be latent and appear only when alkalosis develops following overbreathing The earliest symptoms are paresthesias of the scalp face, and extremities followed by cramp like pains and contractions in the distal

parts of the extremities or the abdominal wall When the parathyroid deficiency is marked there may be tonic and clonic spasm of the muscles particularly of the extremities often of the face trunk larynx and diaphragm and sometimes of smooth muscle such as of the urinary bladder of gastro intestinal tract Blurred vision may occur from spasm of the intra ocular muscles Laryngeal spasm may produce stridor sufficient to cause death from asphyxia In long standing untreated cases cephalic and body hair may fall out the finger nails may become brittle grooved and occasionally may be shed the teeth may show horizontal pit like depressions owing to abnormalities of the enamel and bilateral cataracts may occur frequently Symmetrical cerebral calcification and epileptiform seizures may also occur [38] [7]

This complication of thyroidectomy may be overlooked for a long time if it is mild and associated only with paresthesias or nervous irritability Latent tetany may be detected clinically by (1) *Chvostek's Sign*—spasm of facial muscles on gentle tapping over the facial nerve as it courses anterior to the ear ( ) *Trousseau's Sign*—a characteristic spasm of the hand appearing after five minutes of pressure around the upper arm by a tourniquet or by a blood pressure cuff inflated well above the systolic pressure and (3) *Schlesinger's Sign*—painful spasm of the leg muscles on flexion of the thigh with the lower leg extended Determination of the serum calcium is the most reliable method of establishing the diagnosis Blood levels of total calcium persistently below 9 mg per 100 cc are diagnostic Since calcium exists in the blood partly ionized and partly bound to protein and since the ionized calcium must be depressed before symptoms of hypoparathyroidism appear all atypical cases should also have a determination of the total protein of the blood A decrease in the total protein will be associated with a decreased level of total calcium without alteration in the ionized calcium and therefore without true hypoparathyroidism The normal levels of *ionized calcium* as calculated from the nomogram of McLean and Hastings [7] range from 4 5 to 5 0 mg per 100 cc

The serum inorganic phosphorus may be normal or elevated When this value is high tetany may be induced with only moderate hypocalcemia For this reason both calcium and phosphorus concentrations should be determined when latent tetany is suspected

The incidence of post thyroidectomy hypoparathyroidism is difficult to state because the serum calcium concentration is not determined post operatively in all cases and thus latent cases may be missed Transient decreases in serum calcium levels following thyroidectomy are not un

common but most of these cases do not show the clinical signs of hypoparathyroidism nor do they develop chronic tetany subsequently [9, 31]

Chronic or permanent hypoparathyroidism varies in reported incidence from 0.2 to 5.0 per cent [0] The incidence following secondary operations for recurrent thyrotoxicosis is considerably higher than that following primary operations Bertelsen's studies [0] are among the best since he routinely determined the serum calcium post operatively and followed all cases with hypocalcemia In his series there were 871 primary thyroidectomies and 39 secondary operations with 9 cases or 1.03 per cent of tetany following the primary operations and 1 case or 2.6 per cent following the secondary operations—not enough in the latter case to be statistically valid but agreeing with the experience of others Only one case was transitory the remainder having chronic hypoparathyroidism which required treatment with dihydrotachysterol (A T 10) In addition to this group of 10 cases of established hypoparathyroidism there were 23 cases which showed slight hypocalcemia at the time of discharge from the hospital after thyroidectomy None of these cases had clinical hypoparathyroidism and all had a spontaneous return of normal serum calcium If one considers these as instances of latent transitory hypoparathyroidism the total incidence of parathyroid insufficiency in his entire series would be 3.75 per cent and an incidence of permanent hypoparathyroidism of 0.99 per cent Crile [64] has reported an incidence of postoperative hypocalcemia of 1.5 to 2.0 per cent, depending upon the type of operation, and of permanent tetany of 0.18 to 0.58 also in accordance with the type of operation Cattell's [68] incidence of permanent tetany has been 1.5 per cent in his last thousand operations, there was an equal incidence of transient hypoparathyroidism with spontaneous recovery Goldman [71] has reported an incidence of hypoparathyroidism of 1.5 per cent following operations for toxic diffuse goiter and of 0.5 per cent after operations for toxic nodular goiter

The treatment of post operative hypoparathyroidism depends upon the stage of the syndrome whether acute chronic or latent The aim of treatment in all instances however is to restore the blood calcium to normal levels as quickly as possible and to maintain it at those levels Acute hypoparathyroidism if associated with convulsive episodes or respiratory difficulty requires prompt treatment with intravenous calcium This may be administered as 10 to 20 cc of 10 per cent calcium chloride or 10 to 20 per cent calcium gluconate Simultaneously dihydrotachysterol or vitamin D_2 should be given the former in doses of 4 to 6 cc and the latter in doses of 300 000 to 500 000 units daily Both of these

preparations may be given orally but intramuscular administration is occasionally necessary because of the presence of vomiting Daily serum calcium determinations are essential for the further regulation of the dosage In chronic tetany the restoration and maintenance of normal calcium values will depend primarily upon the use of either vitamin D or dihydrotachysterol A high calcium low phosphorus diet is a useful adjunct but we have not found it so important or so useful as the combined use of vitamin D and orally administered calcium lactate or gluconate Vitamin D in doses of 100 000 to 400 000 units daily combined with 15 to 30 gm of calcium lactate or gluconate will almost invariably restore and maintain normal levels of calcium in the blood Occasional patients have been difficult to manage on this regime fluctuating too readily from states of hypocalcemia to hypercalcemia In these circumstances we have omitted all extra calcium except that normally contained in the diet and have found that vitamin D alone will more smoothly regulate the blood calcium With the aid of weekly or monthly blood calcium determinations the treatment of chronic tetany can be managed without great difficulty When extra calcium is not administered the Sulkowitch test of the urine is useful in the detection of hypercalcemia since the latter condition will readily manifest itself by hypercalcuria

Hemorrhage

Serious hemorrhage during thyroidectomy or post operatively has not been a frequent complication in our experience nor have we observed any mortality from this complication In rare instances however reopening of the incision has been necessary to ligate bleeding vessels A small amount of blood loss within the wound may seriously interfere with respiration and requires instant treatment Cattell[4] routinely reopens the incision when the wound is puffy or ecchymotic to make certain that bleeding is controlled Unexplained respiratory obstruction with intact vocal cords should also be considerd an indication for re examination of the operative site Whole blood transfusions may be necessary when hemorrhage is profuse

Tracheal Obstruction

This complication in rare instances occurs from collapse of a soft trachea following reconstruction of thyroid remnants over the trachea

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The treatment of post-operative hypoparathyroidism depends upon the stage of the syndrome whether acute chronic or latent. The aim of treatment in all instances however is to restore the blood calcium to normal levels as quickly as possible and to maintain it at those levels. Acute hypoparathyroidism if associated with convulsive episodes or respiratory difficulty requires prompt treatment with intravenous calcium. This may be administered as 10 to 20 cc of 10 per cent calcium chloride or 10 to 20 per cent calcium gluconate. Simultaneously dihydrotachysterol or vitamin D_2 should be given the former in doses of 4 to 6 cc and the latter in doses of 300 000 to 500 000 units daily. Both of these

and to combat dehydration. Antibiotic therapy is essential to prevent or control infection. Cold packs and antipyretic drugs will control the hyperpyrexia and restlessness. Oxygen by tent is useful in combatting anoxia, tachycardia and hyperthermia. Sedation with barbiturates or paraldehyde is very helpful in controlling restlessness. In delirious or psychotic patients it may be necessary to utilize these drugs parenterally and in large amounts. Morphine should be avoided because it may aggravate the nausea and vomiting and depress respiration. Meperidine hydrochloride (Demerol) is safer for analgesia or pulmonary edema. Digitalis is not indicated unless auricular fibrillation or congestive failure is present. Cortisone or corticotrophin in large doses may also be useful.

Thyrotoxic crisis usually develops within 4 to 24 hours after thyroidectomy. If it is not controlled by the therapy outlined, a state of shock may ensue which will require transfusions.

Progressive or Malignant Exophthalmos

The development of progressive exophthalmos is one of the rare but serious complications of subtotal or total thyroidectomy for toxic goiter. Apparently it occurs more often after thyroidectomy than after treatment of thyrotoxicosis with the thiouracils or radioactive iodine, but this point is far from established because not enough cases have been treated by medical measures as compared with the many thousands treated by thyroidectomy.

The pathogenesis of exophthalmos and exophthalmic ophthalmoplegia has been discussed above. Most cases appear following the relief of hyperthyroidism when the patient is either euthyroid or hypothyroid. Exophthalmometry has demonstrated that the exophthalmos of toxic goiter rarely recedes following therapy of any type. Lid spasm and weakness of the ocular muscles do improve, however, in most instances, so that the patient appears less exophthalmic. Malignant exophthalmos represents a severe progression of protrusion of the eyeball associated with edema and inflammation of the lids, occlusion of the lachrymal ducts, conjunctivitis and chemosis. There is inability to close the eyelids, which may lead to corneal ulcers and eventually to infection and destruction of the eyeball. Papilledema with decrease of vision or optic atrophy and blindness may occur also. This represents the extreme picture. Intermediate conditions are more common, characterized by proptosis of the globe, conjunctivitis, lachrymation, slight lack of approximation of the lids when asleep, and recurrent corneal ulcers.

This may be remedied by loosening of the sutures In addition Cattell [68] has found that pre-operative hypothyroidism may be followed by post-operative respiratory obstruction of sufficient degree to require tracheotomy This is probably attributable to thickening of the vocal cords and myxedematous infiltration of the larynx When there is respiratory obstruction the patient needs constant supervision until its cause is eliminated or a tracheotomy is performed to establish an adequate airway

Thyrotoxic Crisis

Thyrotoxic crisis or 'thyroid storm' is a rare complication inherently associated with the thyrotoxic state but most often precipitated by thyroidectomy in the inadequately prepared patient Thyrotoxic crisis represents an immense exaggeration of all the features of thyrotoxicosis It is characterized by extreme restlessness irritability, tachycardia flushing sweating, and hyperpyrexia Vomiting, diarrhea and dehydration are common Occasionally there is severe prostration mental apathy and low-grade fever instead of the more usual picture of great activation In the pre-iodine era thyrotoxic crisis was frequent but its incidence has dropped strikingly with the use of iodine for the control of thyrotoxicosis and the pre-operative preparation of the patient

The mortality from thyroid crisis is high at least 50 per cent of patients will be lost regardless of therapy Prevention of this serious complication is therefore most important and may be achieved by bringing patients to operation in a euthyroid state or with no more than mild thyrotoxicosis McArthur, Rawson, Means and Cope [51] found that thyroid storm occurred most frequently in patients with severe thyrotoxicosis complicated by serious diseases, especially heart disease Infections and iodide withdrawal are common precipitating causes of thyrotoxic crisis prior to thyroidectomy

Treatment of thyroid storm should be aimed at the correction of the hypermetabolism hyperthermia infection and dehydration that are the usual symptoms of the process Iodine in large doses must be given either orally or intravenously Lugol s solution in amounts of 15 to o cc daily or equivalent amounts of potassium or sodium iodide should be administered during the first 2 or 3 days with half that amount during the succeeding 7 to 10 days Glucose in concentrations of 10 to 25 per cent in physiological saline in daily amounts of 3 to 4 liters should be administered intravenously to maintain caloric and electrolyte balance,

irradiation must be done with care because of the sensitivity of the eye to irradiation

Protection of the severely exophthalmic eye by the use of glasses ointments eye shields and such minor operations as tarsorrhaphy is most important Expert ophthalmological consultation is essential in directing this phase of the treatment For the patient who continues to progress decompression of the orbit must be considered The usual operation is



A B

Fig 58 B I (BIH No 6,04 A) A 35 year-old man with diffuse toxic goiter and no ocular manifestations Bilateral subtotal thyroidectomy on 9/ 0/41 Progressive exophthalmos with chemosis conjunctivitis and periorbital edema of the right eye started in November 1941 when patient was euthyroid Photographs show appearance of right eye on 3/27 42

that of Naffziger which unroofs the orbit decompression into the frontal ethmoid or maxillary sinuses has also been tried The greatest possible area of decompression is desirable and this can be attained by the intracranial approach advocated by Naffziger [3] In our experience hyperophthalmic thyrotoxicosis has rarely progressed to the point of requiring orbital decompression although one patient had to undergo tarsorrhaphy to preserve the eyeball (see Figs 58 59)

The etiology remains obscure as we have previously indicated but it is certainly related to the syndrome of Graves disease The role of thyrotrophin or indeed of anterior pituitary hormones is unsettled in the human in spite of an established relationship in animals We cannot ourselves accept the point of view that it is less likely to occur following treatment with the thiouracils or radioactive iodine since we have seen instances of mild to moderate progression of exophthalmos following the use of these agents Purves and Griesbach [illegible] have recently investigated the role of thyrotrophin in the causation of malignant exophthalmos by biological assay of human thyrotoxic sera injected into guinea pigs The thyroid gland of the guinea pig was brought to a resting state by the previous administration of thyroid substance and the response of the thyroid evaluated by measuring cell height of the acinar epithelium. They were able to study the sera from 27 cases of malignant exophthalmos and they concluded that thyrotrophic activity was not universally present in the blood of these patients They further assert that pituitary function is normal in thyrotoxicosis While they found that a majority of cases of malignant exophthalmos did have large amounts of thyrotrophin, absolutely typical cases occurred with complete absence of thyrotrophic activity in their serum Similarly very high levels were found in patients with myxedema or euthyroidism induced by thiouracil but without exophthalmos

Methods for the prevention of malignant exophthalmos are uncertain since its cause is unknown However all cases presenting unusual proptosis conjunctivitis and ophthalmoplegia should receive careful exophthalmometry during the course of treatment of the thyrotoxicosis Medical therapy with either stable iodine or the thiouracils allows a gradual induction of euthyroidism and the possibility of resuming a state of mild thyrotoxicosis if there is serious progression of exophthalmos. This same result may be attained however by the administration of desiccated thyroid following thyroidectomy or treatment with radioactive iodine

Our results in the control of severe exophthalmos with the administration of enough thyroid to induce hypermetabolism have not been impressive particularly when used late in the course of the process. Similarly irradiation of the pituitary or administration of iodides has not yielded clear-cut results Irradiation of the orbit however is theoretically useful since malignant exophthalmos is associated with lymphorrhages of the orbital tissues and these cells are probably sensitive to radiation This

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A P

Fig 58 B I (BIH No (7042A) A 55 year-old man with diffuse toxic goiter and no ocular manifestations Bilateral subtotal thyroidectomy on 9/20/41 Progressive exophthalmos with chemosis conjunctivitis and periorbital edema of the right eye started in November 1941 when patient was euthyroid Photographs show appearance of right eye on 3/27 4

that of Naffziger which unroofs the orbit decompression into the frontal ethmoid or maxillary sinuses has also been tried The greatest possible area of decompression is desirable and this can be attained by the intracranial approach advocated by Naffziger [43] In our experience hyperophthalmic thyrotoxicosis has rarely progressed to the point of requiring orbital decompression although one patient had to undergo tarsorrhaphy to preserve the eyeball (see Figs 58 59)

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same etiological factors are operative in both dysfunctions. No definite therapy is available but the condition usually remits after several years. Mills has utilized hyaluronidase injections with beneficial effect in one case.



Fig. 91. Left profile view showing the marked prolapse of the conjunctiva as well as the severe periorbital edema.

Postoperative Hypothyroidism or Myxedema

Myxedema and hypothyroidism represent complications of subtotal thyroidectomy which are undesirable chiefly because they substitute a new disease for pre-existent thyrotoxicosis, and require prolonged supervision and therapy. Their occurrence, however, is an indication of effec

Localized 'Myxedema'

One of the cutaneous manifestations of thyrotoxicosis referred to above consists of localized mucinous infiltrations in the skin of the lower extremities. This has been variously labeled 'localized myxedema,' 'myxedema circumscriptum thyrotoxicum,' and 'solid edema.'[84, 85, 86] It could well be termed 'myxederma,' since it is literally mucin in the skin. Characteristically it appears as single or multiple plaques localized in the



Fig 59 A Malignant Exophthalmos S F (B I H No 71744) 52 year old male with diffuse toxic goiter and moderate exophthalmos treated by bilateral subtotal thyroidectomy on 7/31/43 Progression of exophthalmos began in 1944 when patient was euthyroid The photograph shows the ophthalmopathy as it was seen on 12/13 44 Note the severe chemosis the redundant prolapsed conjunctiva on the left the marked periorbital edema and the ophthalmoplegia Patient had double vision but no involvement of the optic nerve or papilledema

pretibial area sharply demarcated non pitting and tawny or yellowish pink in color. Widening of the hair follicles may produce an appearance like that of pigskin. Occasionally the lesions may surround the lower leg.

This complication is rare but bears an interesting relation to 'malignant' exophthalmos. Like the latter it is most likely to occur following the cure of thyrotoxicosis by either thyroidectomy or the thiouracils. It may also occur during active thyrotoxicosis, however, and is uncommon in true myxedema or hypothyroidism. Curtis and his associates[87] consider it closely associated with progressive exophthalmos suggesting that the



Fig 59 F Right profile view on 10 18 49 Note prominent and tortuous conjunctival blood vessels

edematous regression follows omission of therapy Occasionally patients themselves discover that they no longer require thyroid when through carelessness or other inadvertence they omit the drug Since spontaneous recovery may occur in the occasional patient it is proper to withhold



Fig 59 E. Left profile view on 10/18/49 Note the partial tarsorrhaphy of the temporal portions of the eyelids

Post operative myxedema is ordinarily permanent but occasionally there is enough regrowth of thyroid remnants so that recovery to the euthyroid state occurs These instances may be discovered by the omission of thyroid therapy and observation of the patient since no myx-



Fig 59 F Right profile view on 10 18 49 Note prominent and tortuous conjunctival blood vessels

edematous regression follows omission of therapy Occasionally patients themselves discover that they no longer require thyroid when through carelessness or other inadvertence they omit the drug Since spontaneous recovery may occur in the occasional patient it is proper to withhold

therapy in the mild cases so that the final status of thyroid function may be more quickly determined.

The incidence of post-operative hypothyroidism varies considerably. Recent figures from the Lahey Clinic[69] indicate an over all incidence of 4.5 per cent, but this figure includes some cases that were temporary. Crile's[64] incidence varied from 4.5 to 21 per cent, varying with the completeness of the thyroidectomy. Goldman[71] had the surprising incidence of 29.7 per cent, of which 9.2 per cent were complete myxedema and 20.5 per cent were hypothyroid only.

RADIATION THERAPY OF TOXIC GOITER

Toxic diffuse goiter has been treated by external irradiation of the thyroid gland with roentgen rays and radium, irradiation of the pituitary, and internal irradiation of the thyroid with radioactive iodine.

External Irradiation of the Thyroid

The subject of external irradiation of the thyroid has been well reviewed by Joll[55] who concluded that definite improvement or cure will occur in the majority of cases of early and mild thyrotoxicosis but that in individual cases cure is problematical and requires widely varying intervals of time. Since the susceptibility of thyroid tissue to irradiation has been conclusively established by the use of radioactive iodine, the inherently limiting factor in the application of external irradiation is the intolerance of the skin and other perithyroidal structures to the dosage necessary to destroy or depress the activity of the thyroid cells. Soley and Stone[83] treated 43 patients and effected satisfactory remissions in 25 patients or 58.1 per cent of the total. It took approximately 9 months to achieve euthyroidism in this group of patients. Our own smaller experience has indicated that roentgen ray therapy is slow and uncertain. Bjornboe[99] in a survey of 79 patients followed for 8 to 18 years after x-ray treatment found that two thirds had recurred. All authors emphasize that the delayed response to treatment exposes the patients to the hazards of thyrotoxic crisis, and fatalities from this cause during the course of irradiation therapy are reported by most observers.

The local complications following irradiation of the thyroid gland are serious. Damage to the skin, larynx, trachea and bronchi may be permanent, requiring a lifetime of treatment, and may occasionally result

in fatal asphyxiation from stenosis of the airway.[791] Acute mediastinitis and pericarditis have also been observed by Rose and Wolferth.[79]

Irradiation of the Pituitary

Irradiation of the pituitary in the treatment of thyrotoxicosis has been essayed in a limited number of patients.[79] Thompson[4] produced a permanent remission in one third of 43 cases so treated, but regards the method as potentially harmful to the pituitary and hypothalamus. We have had no experience with this form of therapy.

Internal Irradiation of the Thyroid with Radioactive Iodine

The increased avidity for radioactive iodine of the hyperplastic thyroid gland of Graves' disease provides a means of delivering internal irradiation to thyroid tissue in much larger quantities than is possible by external irradiation with roentgen rays or radium. Radioactive iodine produces both beta rays (short range) and gamma rays (long range). The beta rays are high speed electrons which penetrate to a circumference of several mm. and produce tissue effects similar to x rays or the gamma ray emitted from radium. The gamma rays emitted by radioactive iodine do not primarily influence tissue but do so secondarily by propelling high speed electrons from the atoms of the irradiated tissue, producing tissue damage by ionization of the molecules through which they pass. The amount of damage produced is generally proportionate to the amount of energy absorbed. The gamma rays act over a distance of about 1 meter and are readily measured by the Geiger counter.

Marinelli[79] has utilized the amount of energy absorbed by the tissues to calculate a tissue dose in equivalent roentgen units. As the roentgen by definition and agreement applies only to x or gamma radiation, it can be used for gamma ray emitting isotopes but not for radiation due to primary beta particles. A comparable basis for beta ray dosage can be established, however, if the energy absorbed per gram of air per roentgen is made the unit of energy absorption for beta rays. An equivalent roentgen may therefore be defined as that amount of beta radiation which under equilibrium conditions releases in one gram of air as much energy as one roentgen of gamma rays (Marinelli). The equivalent roentgen or e.r. is essentially the same unit as the rep. or roentgen equivalent physical. Thus the dosage of I^{131} is ordinarily

calculated in terms of equivalent roentgens since the tissue effect primarily results from the emission of beta particles The radiation dosage cannot be measured but it can be calculated *from the half life of the* isotope the radiation energy and the biological uptake and excretion If one assumes that the isotope is homogeneously distributed throughout the thyroid gland and that it remains there throughout its entire process of physical decay then I^{131}, the isotope ordinarily employed would deliver 158 equivalent roentgen units per microcurie of iodine per gram of tissue

This theoretical delivery of radiational energy is decreased by several important factors First homogeneous distribution of the isotope does not occur as radio autographs have abundantly demonstrated Secondly radioactive iodine like stable iodine is incorporated into thyroid hormone and secreted into the blood stream This ordinarily causes a loss of the isotope from the gland at a rate which is greater than that which would occur from physical decay or the theoretical half life The rate of biological subtraction of the isotope from the gland is readily measured in each patient by making periodic counts over the thyroid gland and plotting the disappearance rate From this one may determine the biological or effective half life of the isotope as contrasted with the physical half-life A third factor altering the delivering of the isotope to the tissues is the fact that the periphery of a mass of tissue is not irradiated from all adjacent cells as would be true of the center of the mass

These three variables of heterogeneous absorption biological secretion and decreased irradiation at the periphery do not however significantly interfere with the delivery of large amounts of radiation to thyroid tissue whether normal, hyperplastic or malignant

Paramount consideration must be given to the *dosage of radioactive iodine* since enough must be given to produce a therapeutic effect while avoiding the toxic effects of excessive dosage Four factors enter into dosimetry (1) the amount of radioactive iodine delivered (2) the maximal initial uptake of radioactive iodine by the thyroid (3) the effective or biological half life of I^{131} and (4) the weight of the gland All these factors may be determined with varying degrees of accuracy The amount delivered is readily measured with a Geiger counter The uptake of I^{131} by the gland at any period can be measured with an accuracy of about 5 per cent by the method of Freedberg[149] utilizing a 4 tube technique or with less accuracy by the single tube technique The biological half life may be determined by estimating the loss in

radioactivity from the thyroid gland over a period of several days The weight of the thyroid gland is the factor most difficult to determine with accuracy Experienced observers will differ in their estimations of gland weight by 30 to 50 per cent[296] The inherent error in the estimation of gland weight is therefore large enough to produce significant differences in the end results of therapy Even if it were possible to measure accurately the weight of the gland differences in therapeutic effects will occur as a result of individual variations in the response of patients to radiation[79]

The radiation effects of I^{131} are twofold—upon the personnel handling the isotope and upon the tissues of the patient The hazards to personnel are considerable and require care so that physicians and technicians will not be chronically exposed to harmful irradiation Excessive exposure to irradiation may produce neoplasm depress the bone marrow or cause undesirable genetic effects Osteogenic sarcomas have been produced in man by prolonged exposure to radiation lung carcinoma has been produced by inhalation of radon liver sarcoma by the use of thorotrast and skin carcinoma from gamma rays Evans[79] has pointed out that in all these instances there has been a latent period of 10 to 20 years between the exposure and the appearance of malignancy in addition there has been a prolonged period of exposure over many years to radiation of low intensity In animals tumors of skin connective tissue bone lymph nodes and the intestinal tract have been induced by radiation The possible genetic effects in man have been considered by Evans[79] In animals irradiation increases the number of mutations above those that would occur spontaneously but produces no new type of change In general spontaneous or radiation induced mutations are undesirable Evans calculates that detectable increases in hereditary abnormalities are unlikely even after many generations from radiations up to 0 1 roentgen daily given to a small percentage of the population

The value of 0 1 roentgen daily is considered the maximum allowable exposure to beta or gamma radiation for an individual s lifetime by the National Advisory Committee on Radiation Protection[300] This amount should certainly be considered as the safe upper level of exposure for personnel handling radioactive isotopes In the case of patients subject to tracer or therapeutic doses of I^{131} it would be impossible to use this material for either diagnosis or treatment if this level were not exceeded for a short time An average gastro intestinal x ray examination results in an exposure of about 25 roentgens

The safety factors so far as patients are concerned are twofold (1) the

exposure is transient and (2) I^{131} releases 97 per cent of its radiations within 30 days because of its short half-life, and therefore chronic exposure is avoided

The effects of radioactive iodine upon the tissues of the patient are primarily upon the thyroid gland but may involve other tissues when large doses are used or excretion is delayed These effects have been observed in a small number of patients but have been studied extensively in animals Chapman[301] reports the changes in thyroid tissue removed from 7 patients with thyrotoxicosis who had received radioactive iodine from 19 days to 5½ years previously Nineteen days after treatment the thyroid showed acute cellular injury with cellular swelling and loosening of the follicle cells from the basement membrane Fibrosis was observed in the thyroid 5 months after therapy Fibrosis and regenerative hyperplasia commonly appeared in thyroid tissue removed 1, . and 5 years after therapy In a patient who died of bronchogenic carcinoma 5½ years after radioactive iodine treatment for thyrotoxicosis the thyroid gland at autopsy was firm and fibrotic and weighed 11 gm Histologically it showed fibrosis encircling distorted follicles that contained cells with an increased mean cell height

Complete observations of the effect of varying doses of I^{131} upon the thyroid gland of rats have been made by Chaikoff and his associates[30] Two hundred and fifty rats were sacrificed at intervals of from 6 hours to 8 months after single injections of 4 different doses of I^{131} The initial cytological changes consisted of vacuolation and edema of the cytoplasm Pyknosis and fragmentation of nuclei were also evident among the early changes in the thyroid epithelium These early changes were followed by edema with fibrinous and leucocytic infiltration Within one week reparative processes appeared in the form of proliferating fibroblasts The final histological appearance depended upon the degree of initial destruction With a dose of I^{131} large enough to cause complete destruction of the thyroid the end result at 6 to 8 months was manifest by a band of hyalinized collagenous tissue devoid of all thyroid tissue With smaller doses and failure to damage many of the epithelial cells normal glandular structure was eventually re-established with normal thyroid function In this group however, where there was initial damage but not complete epithelial destruction the picture at 6 to 8 months showed many thyroid cells of abnormal appearance forming small irregular follicles and probably non functioning The very large destructive doses of I^{131} produced some fibrosis in the peripheral portions of the parathyroid glands as well as injury to the trachea and its encircling musculature No

permanent kidney damage was produced but a few of the animals receiving the larger dosage had transitory glomerular congestion and cloudy swelling No liver damage occurred

Gorbman[303, 304] found that toxic doses of I^{131} destroyed the parathyroids of mice even in those instances where it was low enough to permit survival of some thyroidal epithelium The tracheal epithelium was equally sensitive but only the higher amounts injured the recurrent laryngeal nerves Tumorous enlargements in the pituitaries and tracheas were eventually observed in many of these mice

On the basis of doses found radiotoxic to animals Soley[97] has calculated that from 10 to 3500 millicuries would be required to produce total thyroid and parathyroid destruction in man Our own experience with large doses of I^{131} in the treatment of cancer of the thyroid indicates that the parathyroids in the human are more resistant to radioactive iodine than are those in animals

The calculation of I^{131} dosage in terms of equivalent roentgens delivered to the thyroid is based upon the concentration of radioactive iodine within the thyroid as determined by the tracer dose upon the half life of the isotope upon the rate at which the radioactive iodine leaves the thyroid (the biological half life) and upon the estimated weight of the gland These factors are expressed in the following formulas (a) to obtain equivalent roentgens

$$\text{Dose e r} = \frac{\text{MC} \times 160 \times \text{per cent uptake} \times \text{BHL}}{\text{gland weight in grams} \times \text{PHL (8)}}$$

(b) to secure microcuries delivered

$$\text{MC} = \frac{\text{e r} \times \text{PHL (8)} \times \text{gland weight in grams}}{160 \times \text{BHL} \times \text{per cent uptake}}$$

The figure 160 represents the approximate number of equivalent roentgens produced when 1 MC of I^{131} undergoes total decay e r = equivalent roentgens MC = microcuries administered BHL = biological half life in days PHL = physical half life in days i e 8

I^{131} is administered orally in accordance with the dosimetric considerations described Single doses ordinarily have ranged from 4 to 15 millicuries The iodine content in the ordinary dose of I^{131} is equivalent to

exposure is transient and (2) I^{131} releases 97 per cent of its radiations within 30 days because of its short half-life, and therefore chronic exposure is avoided

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toxic goiter except in elderly or bad risk patients because of the possibility of cancer development after 15 or o years Crile and his co workers[306] at the Cleveland Clinic prefer to treat older patients only but feel it is safe to treat younger individuals They recognize that many years must elapse before there can be certainty about the lack of ultimate carcinogenesis Werner and his associates[30] at the Presbyterian Hospital in New York have treated patients as young as 18 years of age Williams[308] has treated patients regardless of age

Our own attitude with respect to age is one of ready employment of radioactive iodine after the age of 40 hesitant use under that age and great reluctance to utilize it before adolescence However we have employed it in one girl of 13 who had both toxic goiter and congenital heart disease and we have also used it in the age groups extending from o to 40 because of recurrent thyrotoxicosis the presence of recurrent laryngeal nerve injury or refusal of surgery by patients not suitable for prolonged therapy with iodides or the thiouracils

All recognize that many years must elapse before there can be certainty regarding the later carcinogenic effects of radioactive iodine The opinion of physicists working actively with these isotopes however affords ample justification for the use of radioactive iodine in the treatment of toxic goiter in most age groups

The type and size of the goiter will also influence the selection of patients for treatment with I^{131} The diffusely hyperplastic goiter is entirely suitable for this type of therapy whereas the toxic nodular goiter is ordinarily less satisfactory Since in the diffusely hyperplastic gland there is high avidity for radioactive iodine throughout the extent of the gland effective internal irradiation can be delivered with prospect of cure of the thyrotoxicosis In the toxic nodular gland however there is ordinarily a non functioning or hypofunctioning nodule surrounded by hyperplastic perinodular thyroid tissue In these circumstances the hyperplastic tissue will be subject to an adequate therapeutic effect from the radioactive iodine but the nodule will take up little or no radioactive iodine Thus one may induce euthyroidism in the patient with toxic nodular goiter but the nature of the nodule remains obscure and presents the usual hazard to the patient of neoplasm pressure and future development of thyrotoxicosis In rare instances toxic nodular goiter represents a hyperplastic and hypersecretory nodule surrounded by hypoplastic thyroid tissue In these conditions radioactive iodine will be taken up selectively by the nodule and much less if at all by the surrounding

the amount of iodine contained in 1/50 000 of a drop of Lugol's solution The dosage in units of millicuries indicates the amount of isotope ingested by the patient The essential unit of dosage is the equivalent roentgen and it is this dosage that is adjusted in accordance with the desired therapeutic result

The selection of patients with goiter for treatment with radioactive iodine will depend in the first instance upon the existence of thyrotoxicosis Radioactive iodine has not yet established itself as a significant therapeutic agent in non-toxic goiters aside from carcinoma of the thyroid The diagnosis of thyrotoxicosis should be securely established by clinical and laboratory methods previously described Therapeutic diagnostic tests with I^{131} are misleading since the response is neither so certain nor so rapid with stable iodine As we have indicated, however the uptake and excretion of tracer doses of I^{131} have become a reliable diagnostic procedure in thyrotoxicosis The tracer dose is an essential part of the therapy of toxic goiter with I^{131} since it is used to determine per cent uptake by the gland as well as the biological half life of the isotope for a given patient Thus any patient in whom the use of I^{131} is contemplated must be traced

Once hyperthyroidism has been unequivocally established other considerations that may validly enter into the choice of patient for treatment will include the following (1) the age of the patient, (2) the type and size of the goiter, (3) the severity of the thyrotoxicosis, (4) the presence of persistent or recurrent thyrotoxicosis after previous thyroidectomy, (5) the presence of recurrent laryngeal nerve paralysis (6) the occupation of the patient, (7) the degree of exophthalmos or the presence of the hyperophthalmic variety of thyrotoxicosis, (8) associated pregnancy (9) associated cardiovascular disease or other complications, and (10) non-avidity of the thyroid gland for radioactive iodine because of recent exposure to or ingestion of stable iodine

1 *The age of the patient* will be a consideration in the use of radioactive iodine until it has been conclusively shown that the usual therapeutic doses of I^{131} are not carcinogenic in the years following treatment Chapman and his associates[301] at the Massachusetts General Hospital initially restricted the use of radioactive iodine to patients over the age of 45 on the basis that life expectancy at this age precluded excessive concern over the late development of cancer Increasing experience however, has led this group to abandon this restriction and now all age groups are treated with I^{131} Trunnell[305] on the other hand argues for great conservatism in the application of radioactive iodine for the treatment of

toxic goiter except in elderly or bad risk patients because of the possibility of cancer development after 15 or 20 years. Crile and his co-workers[306] at the Cleveland Clinic prefer to treat older patients only but feel it is safe to treat younger individuals. They recognize that many years must elapse before there can be certainty about the lack of ultimate carcinogenesis. Werner and his associates[307] at the Presbyterian Hospital in New York have treated patients as young as 18 years of age. Williams[308] has treated patients regardless of age.

Our own attitude with respect to age is one of ready employment of radioactive iodine after the age of 40, hesitant use under that age, and great reluctance to utilize it before adolescence. However, we have employed it in one girl of 13 who had both toxic goiter and congenital heart disease, and we have also used it in the age groups extending from 20 to 40 because of recurrent thyrotoxicosis, the presence of recurrent laryngeal nerve injury, or refusal of surgery by patients not suitable for prolonged therapy with iodides or the thiouracils.

All recognize that many years must elapse before there can be certainty regarding the later carcinogenic effects of radioactive iodine. The opinion of physicists working actively with these isotopes, however, affords ample justification for the use of radioactive iodine in the treatment of toxic goiter in most age groups.

2. *The type and size of the goiter* will also influence the selection of patients for treatment with I^{131}. The diffusely hyperplastic goiter is entirely suitable for this type of therapy, whereas the toxic nodular goiter is ordinarily less satisfactory. Since in the diffusely hyperplastic gland there is high avidity for radioactive iodine throughout the extent of the gland, effective internal irradiation can be delivered with prospect of cure of the thyrotoxicosis. In the toxic nodular gland, however, there is ordinarily a non-functioning or hypofunctioning nodule surrounded by hyperplastic perinodular thyroid tissue. In these circumstances the hyperplastic tissue will be subject to an adequate therapeutic effect from the radioactive iodine but the nodule will take up little or no radioactive iodine. Thus one may induce euthyroidism in the patient with toxic nodular goiter but the nature of the nodule remains obscure and presents the usual hazard to the patient of neoplasm, pressure, and future development of thyrotoxicosis. In rare instances toxic nodular goiter represents a hyperplastic and hypersecretory nodule surrounded by hypoplastic thyroid tissue. In these conditions radioactive iodine will be taken up selectively by the nodule and much less, if at all, by the surrounding

thyroid tissue Euthyroidism and disappearance of the nodule will follow adequate therapy with I^{131}

While most investigators feel that toxic nodular goiters should be treated by thyroidectomy we have utilized radioactive iodine in a small number of patients to render them euthyroid preparatory to thyroidectomy In addition, when surgery appeared risky because of the age or clinical condition of the patient, radioactive iodine has rendered such patients euthyroid and allowed safe postponement of surgery until the patient improved However ultimate treatment of toxic nodular goiter should be with thyroidectomy Radioactive iodine is simply another method of pre-operative preparation, slower than stable iodine and comparable to the thiouracils like the latter it is capable of eliminating the thyrotoxic component in almost all patients with consequent decrease or abolition of surgical mortality

Soley [17] considers *extremely large goiters* with or without pressure symptoms a contraindication to the use of radioactive iodine We have treated patients with such goiters with I^{131} and have observed striking decreases in the size of the goiter but most of these patients have required multiple treatments over long periods of time before attaining euthyroidism For this reason I^{131} is less advantageous than thyroidectomy in this group of patients Surgery leads to euthyroidism more rapidly and while exposing the patient to the usual surgical risks eliminates the hazards of long-standing thyrotoxicosis which is inevitable when multiple doses of I^{131} are necessary

3 *The severity of the thyrotoxic state* is an important clinical consideration in the selection and management of patients for treatment with I^{131} Since severe thyrotoxicosis may readily develop into thyroid storm it is necessary to handle these patients in a manner that will most quickly convert them to a lesser degree of thyrotoxicosis While radioactive iodine occasionally causes extra amounts of hormone to enter the blood stream from the thyroid thus temporarily aggravating or causing thyrotoxicosis this situation occurs chiefly when the normal thyroid gland is exposed to large doses of radioactive iodine We have therefore treated patients with severe thyrotoxicosis with I^{131} but have never used it alone always adding stable iodine with or without the thiouracils within 3 or 4 days after the therapeutic dose of radioactive iodine This interval of time is necessary since too early administration of stable iodine will cause a loss of the administered I^{131} Once the clinical state of the patient has ameliorated the adjuvant therapy with iodides or thiouracils

may be omitted and the patient observed for the effect of radioiodine itself

4 *Thyrotoxicosis that has persisted or recurred* after thyroidectomy represents an elective indication for the use of I [131] The increased morbidity and mortality of secondary thyroidectomy are sufficient to establish non surgical therapy as the optimum treatment in this group of patients Radioactive iodine stable iodine or the thiouracils are therefore the agents among which one may choose Of these radioactive iodine is the most efficient in the production of euthyroidism Dosage calculations may be difficult however since the estimation of the weight of the thyroid remnants is often uncertain

5 When primary thyrotoxicosis or persistent and recurrent thyrotoxicosis is associated with *unilateral recurrent laryngeal nerve injury*, radioactive iodine therapy is again an elective method of treatment which will produce euthyroidism without the risk of bilateral nerve injury

6 *The occupation of the patient* may be important in the utilization of radioactive iodine To singers lecturers and others depending upon a normal voice of proper intensity in their work thyroidectomy always presents the risk of temporary or permanent recurrent laryngeal nerve injury with loss of voice volume or permanent hoarseness For these people I [131] offers an excellent form of non surgical therapy On the other hand in persons chronically exposed to roentgen ray irradiation such as roentgenologists and roentgenological technicians radioactive iodine certainly adds to the radiational hazard and is probably best avoided when such persons require treatment for toxic goiter

7 *Thyrotoxicosis with severe exophthalmos* has been considered an indication for the use of radioactive iodine in therapy by Soley [297] We too originally felt that the slower rate of induction of hypothyroidism by I [131] as compared with thyroidectomy might be advantageous However significant severe progression in exophthalmos following I [131] therapy has been observed by Soley [27] and Werner [309] although Soley considers the incidence to be less than that after thyroidectomy Chapman [311] has observed no progression of exophthalmos We have seen 3 instances of moderate increase in exophthalmos following the use of I [131] in toxic goiter Hyperophthalmic thyrotoxicosis cannot therefore be treated by I [131] with certain avoidance of exophthalmic progression The true incidence of progressive exophthalmos after the use of I [131] as compared with that following thyroidectomy must await larger experience

8 *When thyrotoxicosis is associated with pregnancy* the question of

damage to the fetus, particularly to the fetal thyroid is an additional consideration entering into patient selection Chapman and his associates[310] have studied the uptake of I^{131} in 9 fetuses operatively removed because of maternal disease They found that the fetal thyroid began to collect radioactive iodine from the 14th week on that other tissues did not contain appreciable amounts of I^{131} and that the onset of iodine uptake coincided with the appearance of colloid containing follicles On the basis of this small series one may tentatively conclude that I^{131} therapy is without risk to the fetal thyroid during the first 3 months of pregnancy and that after this period there will be uptake by the fetal thyroid Two pregnant patients treated with I^{131} in the second and sixth months were delivered of normal infants who did not subsequently develop myxedema

9 *Thyrotoxicosis as a complication of serious organic disease or incapacitating mental illness* is ideally suited for treatment with I^{131} In cardiac disease chronic nephritis chronic arterial hypertension hepatic cirrhosis chronic bronchopulmonary disease and severe diabetes mellitus there is increased risk from thyroidectomy in addition one is dealing in these instances with diseases of limited life expectancy Patients with psychoses and severe psychoneurotic states or organic disease of the nervous system such as multiple sclerosis may be poor surgical risks uncooperative and difficult to manage post-operatively For these patients I^{131} offers a simple and effective method of therapy Because of the relatively slow action of I^{131} stable iodides may be needed additionally in the more severely thyrotoxic patients

10 The use of I^{131} to treat toxic goiter may not be feasible despite every clinical indication if the *thyroid gland has slight avidity* for the isotope because of the recent use of stable iodine This may result from the ingestion of iodine-rich foods iodine-containing medicines or the use of iodine-containing radio opaque substances for the visualization of the gall bladder kidneys or other organs Non-avidity cannot remain permanent in the hyperplastic hyperfunctioning gland if exposure to the iodine ceases but the time that must elapse before significant uptake returns will vary Chapman[301] considers two weeks to be adequate but our experience has indicated that it may take many weeks before high uptake returns This could present a considerable difficulty in the management of a patient with severe thyrotoxicosis and a temporarily nonavid gland in whom treatment with I^{131} was desirable

Results of Treatment

The response of patients with toxic goiter to radioactive iodine in therapeutic amounts has been studied and reported in several thousand cases from the year 1946 through the early months of 1954. During this period we ourselves have treated about 400 patients. An adequate experience is therefore available for assessing this therapy in toxic goiter.

The vast majority of patients selected for treatment have had *diffusely hyperplastic goiters* but a small group with *toxic nodular goiters* has also been treated. A significant number of patients with recurrent thyrotoxicosis were treated in all series, including our own, since recurrent thyrotoxicosis is particularly suitable for I^{131} therapy. Most authors have found that patients with toxic nodular goiter do not respond readily to I^{131}, requiring large doses to achieve euthyroidism.[297] Experience with this group of patients is quite small, however. No one reports complete disappearance of well demarcated nodules, unless the nodules are hyperfunctioning. We have employed I^{131} in a small group of patients with toxic nodular goiter and have found responses similar to those observed in patients with toxic diffuse goiter. Nodules have not disappeared or decreased in size. In several patients I^{131} was employed to effect euthyroidism, following which nodules were removed by thyroidectomy.

The problem of dosage of I^{131} has been approached in various ways. The amount necessary to induce euthyroidism has been empirically determined by observation of the effect at different dosage levels. Chapman[301] has attempted cure by the administration of a single dose with impressive results, securing a satisfactory remission in 75 per cent of his cases. Werner[33] also has utilized a single dose and found that radiations greater than 5000 equivalent roentgens were necessary to effect cure. This amount, however, was frequently inadequate and even amounts above 10 000 equivalent roentgens were not always curative. The inevitable error in estimation of gland weight calls for much latitude in the interpretation of these results. Crile[146] has employed a multiple dose system utilizing a small initial dose and determining subsequent dosage by the response to the initial amount after two months. We ourselves have employed a single dose, varying the amount in successive series of patients in accordance with the effects produced as judged by the incidence of euthyroidism, persistence of thyrotoxicosis and transient or permanent myxedema. Our present dosage lies between 6000 and 11 000 equivalent roentgens.

Treatment of thyrotoxicosis by inadequate multiple doses of radioactive iodine is hazardous to the severely toxic patient because it exposes the patient to the dangers of continued thyrotoxicosis without compensating advantages. This is illustrated by the experience of Printzmetal and his co-workers in the treatment of difficult cases of toxic goiter.[311] The single adequate dose permits much safer handling of this group of patients since stable iodine or the thiouracils or both may quickly be added to control the thyrotoxicosis until the internal radiation has taken effect.

In evaluating the results of treatment with radioactive iodine the time interval between treatment and attainment of euthyroidism is of great importance since undue prolongation of thyrotoxicosis may justifiably be considered an adverse effect of any therapy. Radioactive iodine produces euthyroidism within a period of 4 weeks to 6 months, averaging 8 to 12 weeks. Williams[308] found median intervals of 2 to 3½ months in his series, Chapman[301] states that the return to euthyroidism after I[131] averages close to 2 months, and Werner[309] found that 6 to 8 weeks elapsed before euthyroidism appeared. In a small number of patients—7 per cent in Williams' series and 16 per cent in Soley's[305]—intervals beyond 4 to 6 months elapsed before euthyroidism was achieved. These were usually patients with larger goiters and more severe hyperthyroidism. This is in accord with our own experience. An appreciation of the potential tardiness of response is essential in deciding upon further use of I[131] if one is to avoid excessive induction of myxedema or undue radiation hazards.

The over-all results of therapy with radioactive iodine have been excellent and compare more than favorably with those achieved by any previous form of therapy. As a standard of excellent response one should expect a single dose of radioactive iodine to produce normal thyroid function within 3 months. Euthyroidism attained between 2 and 3 months may be classified as good, from the 3rd to the 5th month it may be classified as fair, and beyond the 5th month as poor. When an initial dose does not produce a complete remission, amelioration of the thyrotoxic state ordinarily occurs, and the patient may be safely observed for several weeks after the initial 3 month interval to determine the need for further treatment with I[131]. In Chapman's[301] initial series of 135 patients, 104, or 77 per cent, were cured with one dose, 11, or 8.1 per cent, required 2 doses, and 8, or 5.9 per cent, were improved but still toxic 6 months after treatment. In Werner's series of 103 patients[309] 91.7 per cent, or 89 patients, were rendered euthyroid or hypothyroid after 1 to 3 doses of radioactive

iodine with therapeutic failure of varying degree in 8 patients representing 8 per cent of the total A single dose produced remission in 6, per cent of the patients Feitelberg and his associates[31] in a group of 184 patients of whom 15 had toxic diffuse goiter and 3. had toxic nodular goiter were able to effect cure in 132 or 7. per cent with a single dose 43 or 3 per cent required a second treatment and 9 or 5 per cent had 3 irradiations Their average dose was 10 000 equivalent roentgens or 80 microcuries per gram of thyroid tissue A second series of 106 patients was subsequently treated by the same group with remission in every instance although one patient required 7 treatments with I^{131} Two patients with severe thyrotoxicosis died in storm one because of an inadequate dose of radioactive iodine and the second within 4 hours after the administration of I^{131} Feitelberg and his group favor I^{131} as the standard treatment for all patients with toxic diffuse goiter regardless of age

An adequate dose of radioactive iodine ameliorates most of the signs and symptoms of thyrotoxicosis gradually reducing the thyroid gland to normal size decreasing the basal metabolism and protein bound iodine to the normal range eliminating the cardio vascular thermal and neuromuscular manifestations of the disease Subjective improvement is often apparent after 3 weeks Objective signs of improvement appear shortly thereafter The euthyroidism induced is in every way similar to that produced by other effective agents The eye changes however as with these other therapeutic methods will persist or in a few instances grow worse With complete remission the largest goiters are reduced to normal size provided they are diffusely enlarged goiters containing nodules show shrinkage of the perinodular tissue causing residual nodules to become more prominent *An inadequate dose of radioactive iodine* may produce no amelioration of symptoms may lessen the degree of thyrotoxicosis or may produce temporary euthyroidism with recurrence of activity after several months

The complications of radioactive iodine therapy that have been observed so far are few I^{130} the short lived isotope first used produced radiation sickness when used in large doses This is certainly rare with I^{131} Some patients exhibit tenderness and pain over the thyroid within days to weeks after treatment this too is rare Damage to the parathyroids or the trachea has not been demonstrated in humans An exacerbation of toxicity has been noted rarely by several authors it is presumably due to increased release of hormone into the blood stream we ourselves have not observed this complication Increased exophthalmos or failure to stay the progress of hyperophthalmia has been observed in a

small number of patients by all observers but in this respect radioactive iodine is not worse than and probably not so bad as thyroidectomy or the thiouracils Late development of carcinoma remains as a theoretical possibility

The chief complication of radioactive iodine therapy is the development of myxedema This is either temporary or permanent and usually appears within 3 months after I^{131} therapy but may appear as late as 6 months Transient myxedema may be severe and require treatment with desiccated thyroid In such instances the transient nature of the myxedema can be determined only by the subsequent omission of thyroid When myxedema is partial and the patient can tolerate the hypothyroid state thyroid medication need not be administered while the patient is observed In many instances there is rapid recovery from the hypothyroid state within a few weeks but it may take longer The reported incidence of permanent myxedema varies from about 3 to 17 5 per cent [299, 301, 308, 309, 31, 313] Increasing experience may lead to a decreased incidence of myxedema but errors in estimation of gland weight will remain as the important factor in dosimetry and the complication of myxedema will not always be avoidable

Myxedema is so readily and well controlled with thyroid therapy that it represents a desirable alternative to recurrent or persistent thyrotoxicosis On the other hand it constitutes a serious hazard to the uncooperative or unintelligent or uninformed patient who does not return for treatment of hypothyroidism or who permanently omits thyroid at some later date with return of myxedema and its complications

Complications of Toxic Goiter and Their Treatment

Cardiac Complications

The cardiac manifestations of hyperthyroidism have been discussed above In addition to the alterations in cardiovascular physiology caused by thyrotoxicosis underlying heart disease may be accentuated or uncovered by it arrhythmias may be precipitated and in occasional instances heart failure of any degree may be caused by hyperthyroidism in patients without pre-existent heart disease Patients exhibiting heart failure or arrhythmias associated with thyrotoxicosis have been termed thyrocardiacs This term is ambiguous and we prefer an explicit cardiac diagnosis when this can be established in terms of etiological anatomical and functional states There is however, an important relationship be-

tween hyperthyroidism and co existent heart disease in four ways first toxic goiter seriously aggravates heart disease of every type and may itself produce heart failure and various arrhythmias second mild or even moderate thyrotoxicosis is easily overlooked or its symptomatology masked by associated heart disease third treatment of thyrotoxicosis produces striking amelioration of heart failure and angina pectoris as well as cessation of arrhythmias and actual cure of the myocardial insufficiency due solely to hyperthyroidism and fourth the usual treatment of heart failure angina pectoris and arrhythmias is relatively ineffective until the associated thyrotoxicosis is relieved

While thyrotoxic patients with heart failure or persistent auricular fibrillation usually have associated heart disease of rheumatic hyper tensive or coronary etiology Eggleston[314] has pointed out that cardiac failure of the congestive type may occur from thyrotoxicosis alone in patients with normal hearts This has been well established by the more recent studies of Likoff and Levine[315] and Griswold and Keating[316] These authors have investigated the incidence and types of heart disease in over 1 00 patients with toxic goiter and have come to the same con clusions namely *that congestive failure of minimal moderate or severe* degree may occur from thyrotoxicosis alone Since hyperthyroidism is associated with increased blood volume and increased pulmonary blood flow as well as with ankle edema the diagnosis of congestive failure must be based on such evidence as basal pulmonary rales hydrothorax hepato megaly and massive edema While these criteria have been met in both series it is clear that only about one third of the cases were unequivocally *in severe failure while two thirds had minimal to moderate failure* which therefore might be ascribable to the hydremia of thyrotoxicosis rather than to congestive failure Under any circumstances one is left with an impressive residual of thyrotoxic heart failure In these series from 1_ to 15 per cent of all thyrotoxic patients developed congestive failure of some degree From to 5 per cent of the whole number had some degree of congestive failure on the basis of thyrotoxicosis alone 0 3 to per cent had severe failure In patients with toxic goiter and associated rheumatic hypertensive or coronary heart disease congestive failure was observed in from 50 to 75 per cent of the cases emphasizing sharply the influence of co existent heart disease in the production of failure Of the patients with congestive failure and thyrotoxicosis from 33 to 50 per cent had no demonstrable organic heart disease This represents an extremely high incidence of curable heart disease

The arrhythmias that occur with toxic goiter have been noted above

Permanent auricular fibrillation associated with hyperthyroidism is of double significance first it is much more likely to precipitate severe failure in either the normal or the diseased heart, second it is likely to be associated with underlying organic heart disease Auricular fibrillation is 4 to 5 times more frequent when heart failure is present than when it is absent, in thyrotoxic patients without organic heart disease in whom congestive failure developed the incidence of permanent auricular fibrillation was particularly high Thus Griswold and Keating[316] found permanent fibrillation in more than half of their patients with thyrotoxic congestive failure

When a patient with rheumatic heart disease develops thyrotoxicosis the pre existent heart disease may not be easy to recognize if the patient's cardiac status has not been observed before This is especially true of patients with mitral stenosis Both conditions are associated with accentuation of the first heart sound at the mitral area, with systolic murmurs and an apical thrill The characteristic diastolic murmur of mitral stenosis may be shortened because of tachycardia or auricular fibrillation Even left auricular enlargement or widening of the pulmonary conus may be seen by roentgenography in both conditions The differential diagnosis therefore may be obscure unless there is an associated aortic regurgitation with a characteristic murmur Diastolic murmurs at the aortic area or parasternally are not caused or simulated by thyrotoxicosis and are evidences of underlying organic heart disease An additional factor complicating the differential diagnosis is the frequent association of rheumatic fever and rheumatic heart disease with toxic goiter[317]

In thyrotoxic patients with hypertensive or coronary heart disease the underlying heart disease may be more readily recognized because of the presence of hypertension the more specific roentgenogram of hypertensive heart disease or of left ventricular hypertrophy in the electrocardiogram or because there is angina pectoris or electrocardiographic changes diagnostic of coronary heart disease Thyrotoxicosis may precipitate or intensify angina pectoris in patients with coronary heart disease there is no evidence that hyperthyroidism will by itself produce angina pectoris in patients with normal coronary arteries We have however in rare instances seen classical angina pectoris induced by thyrotoxicosis in comparatively young persons with complete subsidence of the angina for periods greater than a decade following the control of the hyperthyroidism It is very likely that in these rare instances latent coronary insufficiency was made manifest by thyrotoxicosis just as it might be by anemia Ordinarily hyperthyroidism intensifies the frequency of attacks of angina

pectoris and will cause heart failure if the myocardium has been damaged by coronary occlusion

A small group of patients with mild or moderate thyrotoxicosis may present maximal signs of heart disease and such minimal signs of thyrotoxicosis that the hyperthyroidism is overlooked These patients may be treated for heart failure or arrhythmias with poor response and this in itself may initiate diagnostic tests for thyrotoxicosis In these cases eye signs are minimal and the thyroid is not greatly enlarged Such patients tend to be above 45 years of age and are more likely to have nodular goiters with a slow development of thyrotoxicosis The basal metabolism is helpful if there is no heart failure and if there is then tracer studies with radioactive iodine or determination of the protein bound iodine of the blood will be diagnostic

The management of heart failure associated with thyrotoxicosis requires treatment of both conditions the heart failure by digitalis diuretics and diet the thyrotoxicosis by measures that will quickly and certainly produce euthyroidism If there is associated organic heart disease radioactive iodine followed in 4 or 5 days by stable iodine is the treatment of choice since it avoids the high surgical mortality of thyroidectomy reported by most authors in thyrotoxic patients with heart failure Residual nodules that are producing pressure or are suspiciously malignant may be treated surgically after euthyroidism has been established and cardiac compensation restored The maintenance of compensation will be complete if there is no underlying heart disease and no residual thyrotoxicosis The subsequent course of patients with organic heart disease will be dependent upon the nature of the cardiac lesion and will not have been worsened by the thyrotoxicosis Early treatment of hyperthyroidism is most important since congestive failure is more frequent in patients with thyrotoxicosis of prolonged duration

Persistent auricular fibrillation is best treated by digitalis while the patient is thyrotoxic The drug is less effective and larger amounts are required than in fibrillation due to other causes [1, 3] Quinidine is not effective in permanently restoring normal rhythm while thyrotoxicosis is present When euthyroidism is established about one half of the patients with fibrillation will spontaneously revert to normal rhythm In an additional one fourth quinidine will restore normal rhythm the remaining patients will be left with permanent fibrillation since the usual resistance and contraindications to quinidine therapy obtain This applies especially to patients with marked mitral stenosis patients with intractable congestive failure and those with large feebly beating hearts

Diabetes Mellitus and Toxic Goiter

The etiological and physiological relationships between experimental hyperthyroidism and diabetes mellitus have been discussed in Part I. The worsening of diabetes by association with thyrotoxicosis has been previously noted in this Part. The concurrent association of the two diseases is not uncommon: from 1 to 5 per cent of patients with thyrotoxicosis will have true diabetes.[314] The higher incidence appears with toxic nodular goiter; this is not surprising, since patients with this type of goiter are older.

The diagnosis of diabetes in the presence of toxic goiter may be uncertain when the glycosuria and hyperglycemia are border line; this condition is more likely to be associated with mild thyrotoxicosis, for in moderate or severe hyperthyroidism the diabetes is intensified with such marked glycosuria, ketonuria and hyperglycemia that the diagnosis is readily established. Glycosuria is so common in uncomplicated thyrotoxicosis that blood sugar tests will be needed to validate the diagnosis of diabetes. The fasting blood sugar should be at least 150 mg. per 100 cc. of blood before a certain diagnosis is made, and post prandially a rise to 200 mg. or more per 100 cc. of blood is essential before the diagnosis is conclusively established.

Uncontrolled diabetes aggravates the clinical symptomatology of toxic goiter by increasing weight loss and by interfering with proper alimentation and nutrition. On the other hand, the aggravation of diabetes by thyrotoxicosis is more severe and more serious, for hyperthyroidism increases the metabolic demand for calories, thereby promoting ketonuria; it also causes an increased lysing of glycogen from the liver with further hyperglycemia and instability of blood sugar level. The increased amount of circulating thyroid hormone also acts as an insulin antagonist.

The treatment of toxic goiter occurring in a diabetic is no different from the treatment of thyrotoxicosis in general, demanding prompt relief of the hyperthyroid state by effective therapeutic measures. Reported mortality rates from thyroidectomy have been higher than in non-diabetics in earlier series which involved multiple stage operations. With more regular induction of pre-operative euthyroidism by means of the thiouracils and stable iodine, thyroidectomy has presented no increased hazard to the diabetic. Radioactive iodine, however, is particularly useful in this group of patients because it eliminates the hazards of thyroidectomy and simplifies the adjustment of the patient's diet and insulin requirements. The caloric requirements of the thyrotoxic diabetic should

be adequately met so that there will be no combustion of body fat or protein from failure to supply the metabolic demands exogenously the insulin requirements should be similarly met in accordance with the need Thyrotoxicosis significantly depresses the diabetic s tolerance with an increased occurrence of acidosis and coma The coincidence of thyrotoxicosis and coma or impending coma constitutes a double emergency requiring intensive therapy of both conditions Stable iodine in large doses should be given by mouth or intravenously and continued until the diabetes and thyrotoxicosis have been controlled Definitive therapy for the thyrotoxicosis can be undertaken when the diabetes is under control

Pregnancy and Toxic Goiter

Thyrotoxicosis may develop during pregnancy or pregnancy may occur during the course of toxic goiter The incidence of hyperthyroidism in pregnancy is small 0 2 per cent according to Mussey Haines and Ward[319] and thus an etiological relationship is unlikely In addition since there is no significant aggravation of the thyrotoxicosis by pregnancy the hyperthyroidism can be treated without interruption of the pregnancy

The diagnosis of toxic goiter in pregnancy may present difficulties if the hyperthyroidism is mild and not associated with eye changes In normal pregnancy there is slight hypermetabolism and an increased concentration of protein bound iodine to thyrotoxic levels[311, 321] The hyperiodinemia occurs as early as three weeks after conception with values as high as 11 micrograms remaining throughout gestation The basal metabolism does not rise until the second trimester when it may reach as high as plus 20 per cent Since slight hypermetabolism and hyperiodinemia are also characteristic of mild toxic goiter the diagnosis of the latter condition in pregnancy may be difficult The uptake of radioactive iodine in tracer amounts by the maternal thyroid will be as reliable as in the non gravid patient but urinary excretion of radioactive iodine may be misleading if there is uptake by the fetal thyroid This does occur after the fourth month as shown by Chapman[310]

The control of thyrotoxicosis and the production of euthyroidism may be achieved by any of the methods utilized in the non pregnant patient The thiouracils and radioactive iodine however present hazards of unknown extent to the fetus The thiouracils may block synthesis of fetal thyroid hormone with the production of cretinism similarly the

uptake of radioactive iodine might destroy the fetal thyroid with the production of cretinism These objections are theoretical but important because of irreversible developmental damage to the brain and central nervous system in the congenital cretin The *thiouracils* have been used in a small number of patients, whose thyrotoxicosis has been adequately controlled and who have given birth to normal children This has also been true of radioactive iodine in a very small group of patients The treatment of choice for the mildly thyrotoxic patient is however, stable iodine in the usual dosage throughout the pregnancy This therapy may be maintained post partum as a definitive treatment if it has been effective, or may be replaced by other methods if it has not produced and maintained a euthyroid state Patients who are not reasonably controlled by stable iodine may be as readily treated by subtotal thyroidectomy, after preparation with iodide and a thiouracil as the non gravid patient

Thyrotoxic Myopathy

The role of the thyroid hormone in muscle metabolism has been discussed in Part 1, and the nature of the muscle disorder in thyrotoxicosis has been described earlier in this Part Muscle weakness usually occurs in toxic goiter but at times it may be so severe as to overshadow all other symptoms and exhibit a clinical picture that sets it apart In this group of patients the myopathy presents itself in either acute or chronic form

Acute thyrotoxic myopathy with fatal termination from bulbar palsy has been found associated with hyperthyroidism and though the condition is very rare an analysis of the cases indicates a genuine relationship to the thyrotoxic state [3 … 3 3 3 4] The disease is usually fatal and involves particularly the muscles innervated by the cranial nerves The associated signs of thyrotoxicosis are not clearly manifest but hypermetabolism is present and recovery has occurred in a few cases following the use of iodides

Chronic thyrotoxic myopathy is rare but less so than the acute form and non-recognition probably contributes to its apparent infrequency The disorder occurs predominantly in males and the associated hyperthyroidism may be atypical as well as difficult to identify [? 3 3] The syndrome may manifest itself variously but profound muscular weakness occurs in all forms There may occur close simulation of progressive muscular atrophy with tremors muscle wasting fibrillary twitchings and

loss of muscle power and tone without sensory changes or abnormal reflexes[3 6 3 7] The muscular fasciculations are coarser and involve larger muscle bundles than in progressive muscular atrophy where the fibrillation is usually confined to small muscle bundles In other patients striking atrophy of the muscles of the shoulder girdle occurs without fibrillary twitchings or there may be involvement of the small muscles of the hands and feet[8]

Periodic paralysis has also been described in association with thyrotoxicosis but there is apparently no causal relationship although the paralysis may remit with proper treatment of the thyrotoxicosis[8 3 9 3 0]

Other neuromuscular syndromes especially *myasthenia gravis*[331 3] and *myotonic dystrophy*[333] have been found associated with toxic goiter Myasthenia gravis according to McEachern and Parnell[334] may be improved by thyrotoxicosis and worsened by amelioration of the hyperthyroidism This conclusion however is based on observations in only one case

Toxic Goiter in Children and Adolescents

Hyperthyroidism occurring in childhood and adolescence does not differ in its clinical manifestations from the disease as it is ordinarily seen in adults but it does require special consideration because it occurs during the period of development and growth The labile personality of the child and adolescent and the contribution of the thyroid hormone to the growth process introduce difficulties in treatment that are not present in the adult

Juvenile and adolescent thyrotoxicosis is of infrequent occurrence For example only 189 instances were encountered at the Mayo Clinic from 1909 through 1943[33] Bartels found an incidence of 1 per cent at the Lahey Clinic in 1000 consecutive patients[333] Black and Webster[337] found an incidence of 3 5 per cent in a series of 747 patients with Graves disease which included patients up to the age of 18, whereas the Mayo and Lahey Clinic series placed the upper age limit at 14 and 15 respectively The incidence in Black s and Webster s series becomes 1 per cent if patients above the age of 15 are excluded The disease has been described in early infancy but the great bulk of the cases occur between the ages of 10 and 14 As in adults females predominate in a ratio of 5 or 6 to 1 Again as in adults there is a high familial incidence of toxic goiter

uptake of radioactive iodine might destroy the fetal thyroid with the production of cretinism. These objections are theoretical but important because of irreversible developmental damage to the brain and central nervous system in the congenital cretin. The *thiouracils* have been used in a small number of patients, whose thyrotoxicosis has been adequately controlled and who have given birth to normal children. This has also been true of radioactive iodine in a very small group of patients. The treatment of choice for the mildly thyrotoxic patient is, however, stable iodine in the usual dosage throughout the pregnancy. This therapy may be maintained post-partum as a definitive treatment if it has been effective or may be replaced by other methods if it has not produced and maintained a euthyroid state. Patients who are not reasonably controlled by stable iodine may be as readily treated by subtotal thyroidectomy after preparation with iodide and a thiouracil, as the non-gravid patient.

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Acute thyrotoxic myopathy with fatal termination from bulbar palsy has been found associated with hyperthyroidism and though the condition is very rare an analysis of the cases indicates a genuine relationship to the thyrotoxic state.[3, 3, 3, 3, 4] The disease is usually fatal and involves particularly the muscles innervated by the cranial nerves. The associated signs of thyrotoxicosis are not clearly manifest but hypermetabolism is present and recovery has occurred in a few cases following the use of iodides.

Chronic thyrotoxic myopathy is rare but less so than the acute form and non-recognition probably contributes to its apparent infrequency. The disorder occurs predominantly in males and the associated hyperthyroidism may be atypical as well as difficult to identify.[6, 7] The syndrome may manifest itself variously but profound muscular weakness occurs in all forms. There may occur close simulation of progressive muscular atrophy with tremors, muscle wasting, fibrillary twitchings and

level and of the white blood count to avoid inadequate control hypothyroidism and granulocytopenia The difficulties of carrying out such a program in a child or adolescent are considerable both the parent and the child are necessarily involved the time and expense may be great interference with school work is hard to avoid and emotional maladjustment is bound to occur[337] Finally certainty of cure with the thiouracils is probably no greater than in adults For these reasons the thiouracils alone or in combination with stable iodine may not be advantageous in the treatment of moderate or severe hyperthyroidism in children or adolescents

Radioactive iodine has been employed in the treatment of occasional cases of thyrotoxicosis in children and adolescents It is effective therapy producing euthyroidism as in adults Consideration of the life expectancy of the patients in this age group however has deterred more extensive use of this form of therapy because of the potential late hazards of radioactivity

Until the potentially harmful status of radioactive iodine therapy is clarified *subtotal thyroidectomy* in most cases constitutes an effective treatment for juvenile hyperthyroidism It is indicated particularly in cases of moderate or severe thyrotoxicosis as well as in mild cases that have not responded completely to stable iodine Technically the operation is difficult in very young children and severe post operative reactions are likely to occur if pre operative preparation is not adequate The mortality rate of the Mayo Clinic in 109 children operated on since 19[illegible]1 has been [illegible]8 per cent[335] This mortality will undoubtedly be reduced to figures comparable to those in adults by the establishment of euthyroidism pre operatively through the combined use of the thiouracils and stable iodine[33] It is important also to avoid thiouracil induced hypothyroidism pre operatively because of the increased likelihood of respiratory difficulty requiring tracheotomy during thyroidectomy

The amount of thyroid tissue to remove in the child or adolescent has been the subject of disagreement Some surgeons have attempted to avoid post operative myxedema by performing minimal thyroidectomy while others have advocated radical thyroidectomy to avoid recurrent thyrotoxicosis Pemberton[335] advocates the removal of the same proportion of thyroid tissue as in adults In all series the incidence of both persistent and recurrent thyrotoxicosis and of myxedema is greater than in adults The persistent and recurrent cases may frequently be controlled by stable iodine in these cases one may also employ the thiouracils or radioactive iodine Myxedema occurs frequently following thyroidec

The diagnosis of the disease depends upon the usual signs and symptoms of Graves disease The laboratory diagnosis may be difficult in the child because of unsatisfactory basal metabolism tests In these instances determination of the protein bound iodine or tracer studies with radioactive iodine will be helpful The uptake of radioactive iodine by the thyroid of children has been demonstrated to follow the pattern observed in adults—a high uptake in thyrotoxicosis and a low uptake in hypothyroidism More studies with more accurate counting techniques are still needed however in children

Graves' disease in children as in adults may be controlled by stable iodine the thiouracils, radioactive iodine or thyroidectomy The selection and application of the most suitable therapy must take into account the growth requirements of the child, potentially late toxic effects as in the case of radioactive iodine, the traumatic experience of thyroidectomy and the compelling need to establish euthyroidism quickly without prolonged treatment or convalescence and with minimal interruption of the educational and social life of the child or adolescent In addition complications of treatment such as myxedema post operative hypoparathyroidism, and vocal cord damage are more burdensome and difficult to control than in the adult

Juvenile and adolescent hyperthyroidism may be treated with *stable iodine* under essentially the same conditions as in the adult This means that its use should be restricted to mild forms of the disease and to children or adolescents who can be kept under prolonged supervision until the disease has abated If stable iodine does not produce clinical and laboratory evidence of normal thyroid function within a period of 4 to 6 weeks its continued use as the sole method of therapy is unjustified since the patient will be left with partly controlled chronic hyperthyroidism subject to the hazards and disabilities of the disease If euthyroidism is produced by stable iodine its use should be continued as in the adult for that period necessary to produce permanent euthyroidism The detailed management of the patient with mild thyrotoxicosis has been extensively described above

Moderate or severe degrees of thyrotoxicosis in the child or adolescent are not suitable for therapy with stable iodine since rapidity and certainty of cure are unlikely *Treatment with the thiouracils is an alternative* medical treatment that is available for these patients It can control the thyrotoxic state and with prolonged administration for months to years may result in permanent remission However this therapy necessitates frequent observation of the patient for the determination of the metabolic

bring about goiter formation on the one hand and hyperthyroidism on the other In a very small proportion of the cases the nodule itself rather than the non nodular portion of the gland secretes excessive thyroid hormone and is responsible for thyrotoxicosis

Pathology

In most instances the pathology is that of toxic diffuse goiter except for the associated occurrence of single or multiple nodules These nodules in turn show the same pathological changes as occur in non toxic nodular goiters ranging from colloid nodules to benign or malignant neoplasms The hyperthyroid state in toxic nodular goiter results from that part of the gland which is diffusely hyperplastic The nodule itself in most instances has depressed or decreased function Thus its uptake of radioactive iodine is low its capacity to store or secrete hormone is low and enucleation of the nodule or nodules will have no ameliorative effect on the thyrotoxicosis[310]

Cope Rawson and McArthur[311] have demonstrated that the hyperthyroidism in a small proportion of patients with toxic nodular goiter is due to hyperfunctioning hypersecretory single adenomas of the thyroid These present themselves as single nodules in an otherwise atrophic involuted thyroid Pathologically they show hyperplasia which partially involutes after iodine administration They act like hyperplastic thyroid tissue in their increased avidity for radioactive iodine When the nodule has an increased iodine uptake because it is hyperfunctioning the perinodular thyroid tissue involutes and atrophies remission of thyrotoxicosis will therefore occur with removal of the nodule

Symptoms and Signs

In toxic nodular goiter *the thyroid gland* is asymmetrically enlarged by the presence of single or multiple nodules The goiter usually precedes the onset of thyrotoxicosis by many years and the nodules develop in the same manner as non toxic nodules of the thyroid The nodules are therefore subject to such biological changes as hemorrhage cystic generation malignant transformation or substernal descent They may produce pressure symptoms obscuring the underlying thyrotoxicosis Similarly the nodule may be carcinomatous from the beginning and exhibit growth invasiveness and metastasis in accordance with its nature

Nodular goiters associated with hyperthyroidism may be small in size or substernal in location when the hyperthyroidism is mild the diagnosis

tomy in children if recognized it is of course readily treated with no detriment to growth and development Unrecognized post operative myxedema is a serious hazard however and the child requires careful evaluation for many months after thyroidectomy until the final status of thyroid function has been accurately gauged

II TOXIC NODULAR GOITER

Introduction

Definition Toxic nodular goiter may be defined as thyrotoxicosis associated with a nodular goiter Patients with toxic nodular goiter are clinically different from those with toxic diffuse goiter in that they are older have a more insidious onset of hyperthyroidism present fewer eye-signs and are so often mildly thyrotoxic that the disease may be over looked for much longer periods than with toxic diffuse goiter

Synonyms Toxic adenoma and adenomatous goiter with hyperthyroidism are other names for this type of goiter

Distribution and Incidence

Since hyperthyroidism is adventitiously imposed upon a previously nodular thyroid gland the distribution and incidence of toxic nodular goiter follow closely those of non toxic nodular goiter It is therefore more common in goitrous areas and increases in incidence with advancing age The phenomenon of an increasing incidence of toxic nodular goiter in older age groups may be explained by the statistical addition of the usual distribution of thyrotoxicosis and the increasing occurrence of nodules with aging The disease is more common in women but not to the same extent as obtains with toxic diffuse goiter

Etiology

The causes of toxic nodular goiter are at least twofold namely, the factors responsible for nodule formation and those that precipitate thyrotoxicosis In most cases there is no essential link between these two groups of factors and so one actually has two diseases co existent in the same organ Thus the etiologies may be sought in those conditions that

difficult *Hypermetabolism* may be present because of associated heart failure hypertension or uncontrolled severe diabetes The *uptake of radioactive iodine* may be abnormally elevated because of edema or impaired renal excretion or both We have found the *level of the protein bound iodine* in the serum particularly helpful in the diagnosis since it is less affected by extrathyroidal factors Even this test however will be *misleading in patients who have recently* received iodine compounds during roentgenographic examinations

TREATMENT

All the therapeutic methods that are effective in the treatment of diffuse toxic goiter are equally effective in controlling the hyperthyroidism of toxic nodular goiter The nodule however remains unaffected by medical treatment unless it is the rare hyperfunctioning single adenoma which can be as effectively treated by I^{131} as by thyroidectomy The great bulk of the patients therefore require thyroidectomy for the same reasons as do most patients with non toxic nodular goiters

Pre operative preparation should be such as to bring the patient to operation in a euthyroid state This may be accomplished with stable iodine alone or in combination with the thiouracils or with radioactive iodine We have employed radioactive iodine in the treatment of toxic nodular goiter and believe that it has certain advantages It will completely involute hyperplastic areas mistaken for nodules thus eliminating the need for thyroidectomy In the rare cases of hyperfunctioning adenoma complete involution will also occur In all other cases of toxic nodular goiter radioactive iodine therapy effectively involutes the perinodular hyperplastic tissue and may reduce thyroidectomy to simple enucleation of nodules

The operation in all cases prepared with stable iodine or the thiouracils should invariably consist of subtotal thyroidectomy as the minimal procedure since both thyrotoxicosis and the nodules require treatment

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may be overlooked The consistency of the gland varies but it will be much firmer than the diffusely hyperplastic gland of Graves disease if there are multiple nodules present The nodule may fill an entire lobe or it may be concealed by hyperplasia of the perinodular tissue When there is asymmetrical thyroid enlargement and tracheal displacement nodular goiter is almost certainly present even though the thyroid appears diffusely enlarged

The *characteristic eye-signs* of thyrotoxicosis are not pronounced in toxic nodular goiter Brightness of the eyeball stare and lid lag are seen as in Graves disease but moderate or marked exophthalmos is uncommon The cause of the disparity in eye signs between toxic diffuse and toxic nodular goiter is not known perhaps these patients have less of the hypothetical exophthalmogenic factor or inactivate it at a greater rate or respond minimally to its action Clinically the absence of impressive eye-signs contributes significantly to the difficulty in diagnosis

Cardiovascular symptoms are particularly prominent in patients with toxic nodular goiter because they are older than patients with toxic diffuse goiter Therefore there is more associated hypertensive and coronary heart disease, auricular fibrillation and congestive heart failure commonly disguise the underlying thyrotoxicosis Thyroid function therefore needs particular investigation in cardiac patients with nodular goiters so that hyperthyroidism will not be overlooked

Clinical Course

Toxic nodular goiter starts as a non toxic goiter which after many years adds the features of thyrotoxicosis in a gradual and insidious fashion *Sudden onset* of hyperthyroidism *is rare* in this group of patients

Since the *intensity* of the thyrotoxicosis is usually mild the patient tolerates the disease for long periods before appearing upon the clinical scene with associated heart disease or severe diabetes or a progression into a more severe form of the disease precipitated by infection or trauma either physical or psychic

Diagnosis

The diagnosis of toxic nodular goiter is established by the same clinical and laboratory procedures that have been described for toxic diffuse goiter Ordinarily the diagnosis presents no difficulties but when the thyrotoxicosis is mild or atypical the evaluation of thyroid function may be

difficult *Hypermetabolism* may be present because of associated heart failure hypertension or uncontrolled severe diabetes The *uptake of radioactive iodine* may be abnormally elevated because of edema or impaired renal excretion or both We have found the *level of the protein bound iodine* in the serum particularly helpful in the diagnosis since it is less affected by extrathyroidal factors Even this test however will be misleading in patients who have recently received iodine compounds during roentgenographic examinations

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PART VIII

MYXEDEMA, JUVENILE HYPOTHYROIDISM AND CRETINISM

MYXEDEMA

Introduction

Definition Myxedema is the disease state resulting from complete or partial lack of the thyroid hormone The hormone deficiency may develop from primary disease of the thyroid from drugs that inhibit hormone synthesis from internal or external irradiation and from thyroidectomy In addition it may be secondary to hypopituitarism with failure of thyrotrophin production The myxedematous state is characterized by generalized mucinous infiltration of the tissues

Synonyms Hypothyroidism athyreosis and Gull's Disease are commonly used synonyms

Historical Although the relationship between absence of the thyroid gland and cretinism had been clearly described in 1850 by Thomas Blizard Curling[1] it was not until 1873 that Sir William Gull delineated the clinical picture of adult myxedema without however definitely suspecting its cause Ord[3] in 1878 first applied the term myxedema to the disease The surgeons Reverdin[4] and Kocher in 1882 and 1883 respectively unequivocally established the relation of myxedema to the thyroid by describing cachexia strumipriva following thyroidectomy for goiter Finally the Clinical Society of London stimulated by Gull's description of adult myxedema thoroughly investigated the extant knowledge of the disease and in 1888 published its classical monograph summarizing the essential etiology and pathology of the condition and emphasizing the identity of cretinism myxedema and cachexia strumipriva[6]

Incidence and Distribution

Myxedema occurs about 5 times more frequently in women than in men and is increasingly common after the age of 30 There is no familial

tion of the thiouracils however will show characteristic hyperplasia of the acinary epithelium and decreased colloid The pathological changes in the thyroid when myxedema is associated with endemic or sporadic goiter are similar to those observed in the goiters of cretins varying from hyperplastic to involuted glands and often showing areas of atrophy and fibrosis

The pathological changes produced by myxedema in *tissues other than the thyroid* are similar regardless of the etiology of the hypothyroidism except with regard to the pituitary In myxedema secondary to hypopituitarism *the pituitary* will show atrophy and fibrosis or a tumor causing compression and atrophy of the hypophyseal tissue In myxedema resulting from primary disease of the thyroid *the anterior pituitary* usually shows some enlargement Histologically there is an increase in the number size and degree of vacuolization of the basophilic cells associated with hypoplasia of the eosinophilic cells[11]

Pathological change in the *remaining endocrine glands* is not significant the paucity of autopsied cases of myxedema may be responsible for inadequate study of these changes

Characteristically myxedema produces *edema* not only in the skin where it is clinically apparent but also in many of the body tissues The *skin* is hyperkeratotic with marked edema in the corium causing a separation of collagen and elastic fibers *Atrophy* may develop in long standing cases The *heart* shows edema of the muscle fibers *pericardial effusion* is not uncommon clinically or at autopsy [1] There may be pleural effusion as well as massive ascites[13] Kountz[14] regards hypothyroidism as a significant factor in the production of *medical arteriosclerosis* in the aorta and larger blood vessels He bases this conclusion on autopsy findings in four patients who had undergone total thyroidectomy for cardiopulmonary disease and who subsequently died of rupture of the aorta Foster and Barr[15] have described extensive lesions of the *muscles* in long standing untreated myxedema These consist of degeneration of the central portion of the sarcoplasm with the production of vacuoles containing a basophilic material either granular or homogeneous This lesion was found in cardiac and skeletal muscles and in the muscular layers of the esophagus gall bladder urinary bladder and uterus

Pathological Physiology

The altered physiology of myxedema occurs as a consequence of the

incidence as in hyperthyroidism except in areas of endemic goiter, where iodine-deficient goiters associated with hypothyroidism may afflict several members of a family

Etiology

Myxedema may result from 'idiopathic' atrophy of the thyroid gland or from hypoplasia after acute or chronic thyroiditis It may supervene after thyroidectomy for toxic or non toxic goiter or be intentionally induced by total ablation of the normal gland[7] Internal radiation with radioactive iodine may induce it in either the normal or the hyperplastic gland[8], it has followed external irradiation of the thyrotoxic gland but not of the normal thyroid[9] It may be induced by drugs that interfere with iodine uptake or hormone synthesis such as the thiouracils or the thiocyanates, in either the hyperplastic or the normal thyroid Rarely, it is temporarily induced by stable iodine in the therapy of toxic goiter particularly if there is an associated thyroiditis Endemic goiter and rarely, sporadic goiter may be associated with myxedema In these circumstances iodine deficiency prevents synthesis of an adequate amount of thyroid hormone, subnormal levels of hormone provoke excessive secretion of thyrotrophin, which stimulates the thyroid to produce large amounts of colloid poor in thyroxine content, thus both goiter and myxedema ensue Finally myxedema may follow hypopituitarism from any cause when inadequate production or secretion of thyrotrophin impairs the integrity of the thyroid[10]

Pathology

The pathological changes in the *thyroid gland* in myxedema will depend upon its etiology The extrathyroidal pathology however will be essentially the same regardless of etiology, except in pituitary myxedema In primary or idiopathic myxedema the thyroid parenchyma is so shrunken that the total gland weight is markedly reduced The thyroid follicles are replaced for the most part by fibrous tissue and lymphocytic infiltration, the remaining follicles are usually inactive lined with low epithelium containing colloid in various amounts or none at all The degree of fibrosis and lymphocytic invasion will vary with the stage and duration of the disease In myxedema following thyroiditis or internal radiation with radioactive iodine the end picture is little different from that seen in primary atrophy Myxedema associated with the administra

The response of euthyroid subjects [illegible] markedly from that noted in hypothyro[illegible] tion between the amount of thyroid ad[illegible] the basal metabolism In euthyroidism the blo[illegible] at normal levels with doses of thyroid that ca[illegible] in myxedemics If however thyroid is given in do[illegible] (6 to 8 gr) daily both the blood iodine and the ba[illegible] become elevated in many subjects the metabolic resp[illegible] the serum iodine but ultimately becoming parallel [illegible]

The stability of the blood iodine in euthyroidism and [illegible] to administered thyroid suggests to Riggs and his associates [illegible] vating mechanism in the normal thyroid They feel that the norma[illegible] can inactivate exogenous hormone by degradation of hormonal [illegible] to inorganic iodine through a reversal of the normal processes that [illegible] to incorporation of inorganic iodine into hormonal iodine

A contrary view has been advocated by Greer [illegible] in a study of the effect of desiccated thyroid on the function of normal human thyroid Utilizing radioactive iodine as a tracer he found that the daily ingestion of 195 mg (3 gr) of U S P thyroid depressed I^{131} uptake to near myxedema levels in about one week in most subjects although one patient required greater amounts for a longer period The recovery of the normal thyroid from a depressed state of I^{131} uptake following the omission of exogenous thyroid was both complete and rapid regardless of the time during which thyroid was administered the majority of subjects had attained normal avidity for iodine after [illegible] weeks although one did not recover completely until 11 weeks after omission of the thyroid medication This depression of the thyroid s iodine trapping mechanism was not due to the iodine content of the administered thyroid since ingested iodine in equivalent amounts had no effect The chief cause of the decrease in thyroid function produced by exogenously administered thyroid may be ascribed to inhibition of thyrotrophin secretion by the pituitary gland

Following the omission of thyroid as the gland function returns I^{131} uptakes in the thyrotoxic range may occur in subjects who have taken thyroid for several years

Greer [illegible] feels that there is no increased sensitivity to exogenous thyroid in myxedema It is well established that increasing doses of thyroid have a decreasing effect upon the basal metabolism in myxedema as the metabo-

decrease or absence of thyroid hormone. This produces widespread effects upon iodine metabolism, total metabolism, intermediary metabolism, water balance and the circulation.

Iodine Metabolism

In myxedema the amount of circulating hormone is greatly reduced; this reduction is reflected in the characteristically low level of protein-bound iodine in the blood. The average level of 'hormonal' iodine in myxedema is somewhat less than half the normal value; it rarely approaches the absolute zero which should be expected in athyreosis. In untreated hypothyroidism the protein-bound iodine of the blood is regularly subnormal. It is also temporarily depressed in the blood of euthyroid subjects who have recently stopped taking desiccated thyroid; this may well represent inhibition of endogenous thyroid hormone production. Finally there is a subnormal level of blood protein-bound iodine following thyroidectomy for hyperthyroidism; this lowering probably reflects the temporary state of mild or moderate hypothyroidism that follows adequate surgery. After total thyroidectomy and in myxedema induced by the use of thiouracil during the treatment of patients with thyrotoxicosis serum iodine values not significantly greater than zero may be found. There is, however, no strict parallelism between the clinical degree of myxedema and the amount of decrease in blood iodine. But if the analytic results are reliable and the patient has not recently received organic iodine for diagnostic roentgenography or desiccated thyroid for treatment, the finding of a normal level of serum 'hormonal' iodine would strongly exclude the diagnosis of myxedema.

When hypothyroid patients are treated with desiccated thyroid the serum protein-bound iodine is readily elevated in quantitative fashion, contrasting with the response of euthyroid subjects who are resistant to alterations in the blood iodine level by this means. In hypothyroid patients 60 mg (1 gr.) daily of thyroid will cause an elevation of 0 gamma per cent in the blood iodine level, 180 mg (3 gr.) of thyroid daily elevates the blood iodine to normal values and maintains it there, thus suggesting that the daily production of endogenous hormone is equivalent in iodine content to 180 mg (3 gr.) of U.S.P. thyroid. This is biochemical confirmation of our own clinical findings that 180 mg is the usual dose of desiccated thyroid required by myxedemic patients for complete relief of their symptoms.

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The response of euthyroid subjects to thyroid administration differs markedly from that noted in hypothyroidism There is lack of correlation between the amount of thyroid administered and the effect upon the basal metabolism In euthyroidism the blood iodine tends to remain at normal levels with doses of thyroid that cause significant elevations in myxedemics If however thyroid is given in doses of 360 to 480 mg (6 to 8 gr) daily both the blood iodine and the basal metabolism will become elevated in many subjects the metabolic response lagging behind the serum iodine but ultimately becoming parallel [16, 17, 18]

The stability of the blood iodine in euthyroidism and its resistance to administered thyroid suggests to Riggs and his associates [19] an inactivating mechanism in the normal thyroid They feel that the normal gland can inactivate exogenous hormone by degradation of hormonal iodine to inorganic iodine through a reversal of the normal processes that lead to incorporation of inorganic iodine into hormonal iodine

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lism rises from completely myxedemic levels to the normal, so that a plateau is reached as the metabolism becomes normal (Fig 60) Above this level Greer believes there is no difference in the response to administered thyroid among subjects with or without intact thyroid glands

The metabolism of iodine in myxedema has been studied by means of the uptake and excretion of radioactive iodine In complete athyreosis

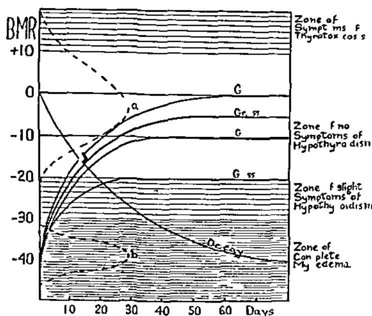


Fig 60 Diagram showing the approximate relationships among metabolic levels symptoms and thyroid rations The dosage is indicated in grains of thyroid U S P given once a day The curves so labeled indicate what may be expected to happen in the way of calorigenic response when the several rations are given to patients with complete myxedema The curve labeled decay indicates the metabolic response which may be expected when one discontinues the administration of thyroid to a patient with myxedema whose metabolic rate was maintained at a standard level or when one completely extirpates the thyroid gland of a person with a standard metabolic rate The frequency curves plotted against the basal metabolic rate at the left are *(a)* for persons with no thyroid disease and *(b)* for patients with spontaneous myxedema Reproduced *from Means J H and Lerman J Arch Int Med 1935* LV 1

whether spontaneous or after thyroidectomy for toxic goiter, the uptake of radioactive iodine in the thyroid region is very low, varying from zero to the lowest level of normal about 15 per cent Our own experience is indicated in Table VIII Keating and his associates [1] have found no difference between spontaneous and post thyroidectomy myxedema so far as thyroid uptake and renal excretion are concerned The urinary

excretion of radioactive iodine in myxedema is slowed so that a larger period of observation is necessary to establish the almost quantitative excretion of I 131 which is characteristic of the disease Uptake studies over the gland 24 hours after administration are however maximal and therefore diagnostic

TABLE VIII

THE UPTAKE AND EXCRETION OF RADIOACTIVE IODINE IN MYXEDEMA

Case	*Sex*	*Thyroid Uptake per cent*	*24 hr Urinary Excretion per cent*	*Type of Myxedema*
1	F	11.0	54.0	Idiopathic
2	M	11.0	37.0	Idiopathic
3	M	11.0	53.0	Idiopathic
4	F	6.0	66.0	Post I 131 Therapy
5	F	12 5	—	Idiopathic
6	F	9.0	55.0	Post I 131 Therapy
7	F	13.0	53.0	Idiopathic
8	M	13.0	59.0	Idiopathic

In myxedema secondary to hypophysial deficiency the functional atrophy of the thyroid is evidenced by uptakes of I 131 which are in the myxedemic range

Myxedema is a frequent sequela of thyroiditis but the iodine accumulating function of the gland in thyroiditis has proved somewhat paradoxical In the acute and subacute forms a clinically euthyroid state ordinarily exists in association with an I 131 uptake and excretion characteristic of myxedema [1] [3] In chronic thyroiditis the response to I 131 is confusing In Hashimoto s thyroiditis or struma lymphomatosa Keating [1] has found entirely normal iodine accumulating function associated with frank clinical myxedema In Riedel s struma however the uptake of I 131 was far lower than normal although not quite myxedematous and was associated with clinical euthyroidism

The evaluation of the iodine accumulating function of the thyroid gland in myxedema with I 131 requires consideration of the effect of preceding administration of desiccated thyroid or of stable iodine upon this function Desiccated thyroid depresses the uptake of I 131 by the thyroid in euthyroid individuals to myxedematous levels this depression

may persist for many weeks or even months after its omission [illegible] Similarly the administration of stable iodine by mouth to euthyroid subjects depresses the uptake of I^{131} to myxedematous levels and this low uptake may persist for weeks or months after its omission Pyelography and especially cholecystography with the use of iodine-containing dyes similarly may depress I^{131} accumulation in the thyroid This effect may last up to a year or longer and is therefore of considerable diagnostic significance when I^{311} is employed

Metabolic Level in Myxedema

While depression of the basal metabolism is characteristic of myxedema, it is not specific or invariable In this regard, there is an important difference between myxedema and thyrotoxicosis the latter is almost always associated with an elevation of the basal metabolism but clinical myxedema may occur with metabolic rates above the myxedemic zone This situation may be encountered when myxedema is associated with hypermetabolism of non-thyroid origin as in hypertension or heart disease The non-specificity of hypometabolism as a diagnostic finding in myxedema is further indicated by its occurrence in undernutrition anorexia nervosa and nephrosis

The development of the characteristic hypometabolism of myxedema has been studied in two ways first by the omission of thyroid in patients with spontaneous myxedema maintained at euthyroid levels second by observations on the basal metabolism in euthyroid patients who have undergone total thyroidectomy for heart disease More recently the development of myxedema in euthyroid and thyrotoxic patients following the use of the thiouracils and radioactive iodine has afforded additional data concerning the metabolic level of hypothyroidism

If desiccated thyroid is omitted in a myxedemic maintained at a normal level of metabolism the basal metabolism falls progressively in a gently sloping curve over a period of 70 to 80 days from a level of zero to a level of about minus 40 per cent This decline represents the physiological response to the decay of previously ingested thyriod Twenty days following the omission of thyroid the basal metabolism drops to levels of about minus 20 per cent and mild symptoms of hypothyroidism appear after 40 days levels of about minus 30 per cent and more marked hypothyroid symptoms will obtain, from the fortieth to the eightieth day there occurs a further slow decrease to levels of about minus 40 to 45

per cent This is the metabolic level of complete myxedema[23] (Fig 60) The relation of the metabolic level to clinical symptoms is not of course as precise in every patient and in fact requires particular consideration

Blumgart and Davis[7] have studied the development of hypothyroidism after complete removal of the normal thyroid gland They found a consistent and gradual decrease in the basal metabolism in such patients by the end of the twentieth day the basal metabolism had dropped to almost minus o per cent From this point on the rate of decrease does not parallel the curve of normal decay but decreases at a much slower

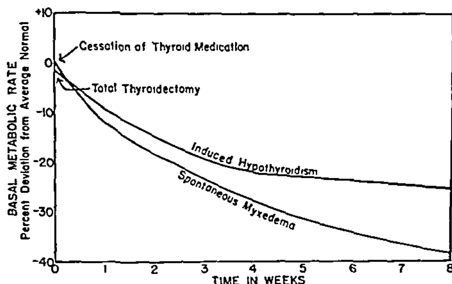


Fig 61 The average rate of decrease of basal metabolic rate following total ablation of the normal thyroid gland as compared with average decrease following omission of thyroid therapy in spontaneous myxedema patients, whose basal metabolic rate had been brought to the standard normal level by thyroid medication The curve for the spontaneous myxedema group is from Means and Lerman (13) the curve following total thyroidectomy is based on an analysis of our first fifty consecutive thyroidectomized patients. Reproduced from Blumgart H L and Davis, D Endocrinology 1934, xviii 693

rate and eventually levels off at about minus 5 per cent at the end of 60 days (Fig 61) However some of these patients did reach metabolism values as low as minus 41 to minus 47 per cent This failure of parallelism between the decay curve of spontaneous and induced myxedema may

well be due to minute remnants of functioning thyroid tissue left behind at operation or, more probably, represents the underlying effect upon the metabolism of associated heart disease or hypertension

The induction of hypothyroidism for the relief of heart disease in euthyroid patients through the use of I^{131} has been accomplished by Blumgart and his associates[8] Symptoms and signs of myxedema were noted as early as five weeks or as late as five months after the administration of radioactive iodine An average total dose of 55 millicuries was required to induce myxedema The rate of fall of the basal metabolism as hypothyroidism developed did not follow the pattern seen after total thyroidectomy or that noted after omission of thyroid medication in patients with myxedema The rate of development of hypothyroidism was more variable, as would be expected from the tissue effects of I^{131}

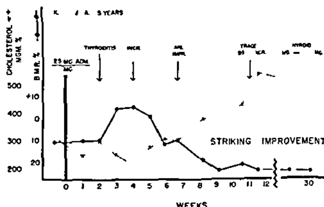


Fig 62 J K Case 3 The serum cholesterol the basal metabolic rate and the clinical course following the administration of 42 5 millicuries I^{131} To conform to the activity of the millicurie used by the Bureau of Standards and also used throughout this paper the millicurie stated in the above figure should be multiplied by the factor of 1 7 Reproduced from Blumgart H L., Freedberg A S and Kurland G S Circulation 1950 1 1105

The hypothyroidism that finally materialized however could not be differentiated from post-thyroidectomy myxedema so far as the level of basal metabolism was concerned Basal metabolism values as low as minus 42 per cent were reached but most of these patients were frankly myxedemic at metabolism levels of about minus 25 per cent Here again associated heart failure or hypertension probably prevented the expected decrease to levels of metabolism more characteristic of complete myxedema (Fig 62)

When desiccated thyroid is administered to an athyreotic individual

the rate of increase in the metabolic level mirrors the rate of decrease of metabolism which follows omission of thyroid in such a patient Thus the administration of 180 mg (gr 3) of U S P thyroid will elevate the metabolism from minus 40 to minus 20 per cent at the end of 10 days to minus 10 per cent at the end of o days and to zero at the end of 60 days On the fortieth day the metabolism will have risen to about minus 5 per cent in a zone of unquestioned normality on the fortieth day after omission of thyroid the metabolism will have dropped just below minus 30 per cent in a zone of unquestioned myxedema[24] (Fig 60)

Water Exchange and Adrenocortical Function

The relation of thyroid function to water exchange has been discussed in Part 1 Myxedema is regularly associated with increased water retention in the extracellular space and a decreased plasma volume The tissue fluid of myxedema is distinctive because of its high content of a mucinous protein the total protein concentration is twice that of serum The diuresis that follows thyroid administration in the myxedemic patient is of large magnitude and is associated with a considerable sodium and nitrogen loss The increased capillary permeability in myxedema contributes further to the increased extracellular fluid and decreased plasma volume

Several of the functions of the adrenal cortex are altered in myxedema The urinary excretion of neutral 17 ketosteroids an indicator of adrenal androgen production is ordinarily decreased especially in long standing untreated cases Thyroid medication may restore the 17 ketosteroid values to normal in pre menopausal women but not in post menopausal women or in men The greatly altered water metabolism of myxedema is not clearly related to the function of the adrenal electrolyte hormone since concentrations of serum sodium potassium and chlorides are usually normal in myxedema The excretion of adrenal corticosteroids a measure of the adrenal sugar hormone may be somewhat depressed in myxedema but this finding is not so regular as the depression of 17 ketosteroids [4]

Protein Metabolism

In myxedema there is protein storage as evidenced by decreased urinary nitrogen This protein storage occurs in the extracellular fluid in the form

of a mucinous protein which is excreted or oxidized when thyroid is a
ministered Plasma and spinal fluid protein are greatly increased

In both thyrotoxicosis and myxedema alterations occur in the metab

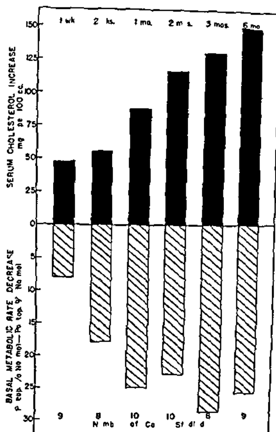


Fig 63 Relationship between the average changes in the serum cholesterol concen tration and average changes in the basal metabolic rate following total thyroidectomy The values presented were obtained in patients on whom both measurements were mad preoperatively and who after operation had not yet received thyroid medication In 2 of the 6 patients whose cholesterol concentrations were measured one week afte operation the basal metabolic rates for the period were obtained by interpolation from the values obtained pre operatively and two weeks post operatively The average pre operative basal metabolic rate for all cases represented was minus 4 per cent and the average serum cholesterol value was 174 mg per hundred cc Reproduced from Gilligan D R Volk M C Davis D and Blumgart H L Arch Int Med 1934 LIV 746

lism of creatine In thyrotoxicosis creatine is excreted in abnormal amounts in myxedema there is storage of creatine in the muscles The usual creatinuria of normal children is reduced or absent in cretinism and

juvenile myxedema thus indicating the role of the thyroid hormone in the regulation of creatine metabolism The administration of small amounts of desiccated thyroid to myxedematous patients causes significant creatinuria which eventually returns to normal levels with continued ingestion of thyroid This response of creatine metabolism to thyroid medication may be regarded as an excretion of stored creatine or phosphocreatine from the muscles

Fat Metabolism

Myxedema usually alters the lipid metabolism so as to cause an elevation in the cholesterol cholesterol esters fatty acids and phospholipids of the blood The neutral fat level however is unchanged Gofman and his associates [8] have demonstrated by analytical ultracentrifugation that the majority of patients with hypothyroidism have an elevation of blood lipids in the Sf 10-20 class This class includes the lipid group that is also elevated in patients with myocardial infarction and nephrosis

Before the development of such specific tests of thyroid function as the determination of the blood protein bound iodine or the uptake of radioactive iodine by the thyroid gland the alterations in the serum cholesterol in myxedema provided a useful but non specific diagnostic and therapeutic guide Statistically there exists an inverse relation between the serum cholesterol level and thyroid function as measured by the basal metabolism The excellent studies by Gilligan and her co-workers [7] have demonstrated this relationship most graphically in myxedema following total thyroidectomy for heart disease (Fig 63) They pointed out however as had others that in a given patient there existed no precise quantitative relation between the increase in serum cholesterol concentration and the decrease in basal metabolism

The lack of this quantitative relationship has led to a renewed evaluation of the serum cholesterol in myxedema In the first instance studies in large groups of normal subjects have indicated a significant though not obligatory rise in the values with increasing age so that increases above 300 mg may be found in a small percentage of normal persons [illegible] Secondly instances of profound myxedema with normal blood cholesterol have been observed The administration of desiccated thyroid depresses the level of the serum cholesterol in hypothyroidism regardless of its initial value This response to thyroid medication in myxedema is in itself of diagnostic value

Peters and Man[30] have further clarified the relation of serum cholesterol to thyroid function by comparing the concentration of serum precipitable iodine with that of the serum cholesterol in patients with and without thyroid disease In hyperthyroidism they found the serum cholesterol so frequently within the wide limits of normal as to be of little diagnostic aid in an individual patient Amelioration of the thyrotoxicosis will be followed by a rise in the blood cholesterol The serum cholesterol responded more rapidly than the basal metabolism or the protein-bound iodine when myxedemic patients were treated with desiccated thyroid so that normal serum cholesterol values occurred before there was an appreciable effect upon these other criteria of thyroid activity In hypopituitary myxedema normal levels of serum cholesterol were found this may have resulted from the associated malnutrition

Carbohydrate Metabolism

In myxedema there is a decreased rate of absorption of glucose from the intestinal tract so that the oral glucose tolerance curve is low and flattened Co existent diabetes is rare Total thyroidectomy ameliorates existent diabetes by lowering the total metabolism and perhaps also by eliminating any diabetogenic action of thyroid hormone[31 3]

Vitamin Metabolism

In myxedema the metabolism of vitamin A is significantly disturbed since thyroid hormone is necessary for the splitting of carotene into Vitamin A and for facilitating liver storage of this vitamin Thus in hypothyroidism an increased amount of carotene occurs in the blood serum and imparts to the skin a slight yellowish tint

The Blood in Myxedema

Since thyroid hormone is essential for normal blood formation anemia occurs regularly in both human and experimental hypothyroidism In the rat and rabbit a normochromic and slightly macrocytic anemia develops after thyroidectomy The ability to regenerate red cells and hemoglobin following hemorrhage is decreased In human subjects following total thyroidectomy Stern and Altschule[33] noted the development of a slightly hyperchromic macrocytic anemia as the basal metabolism declined Bomford[34] has found macrocytic anemia of moderate

degree to occur commonly in myxedema poikilocytosis and anisocytosis are uncommon and hematopoesis is depressed as indicated by a hypoactive bone marrow Occasionally a hypochromic anemia may develop if there is also iron deficiency and more rarely there may be an associated true Addisonian or pernicious anemia

Bomford regards the common macrocytic anemia of myxedema as a result of a decrease in size of the erythroblasts responding to the diminished tissue demand for oxygen The bone marrow thus shrinks in size and cannot respond quickly with a shower of reticulocytes as does the bone marrow of maturation arrest typical of pernicious anemia when their respective defects are corrected Desiccated thyroid in adequate amounts will correct the usual macrocytic anemia of myxedema for patients with hypochromic anemia iron must also be added and for those with Addisonian anemia liver extract or vitamin B_{12} must be given in addition to thyroid

Cardiovascular Dynamics

Zondek in 1918 first applied the term myxedema heart to four cases of myxedema exhibiting cardiac enlargement feeble heart action and electrocardiographic abnormalities with reversion to normal following the administration of thyroid[5] He made no mention of heart failure in association with these alterations in cardiac function but Fahr[36] and later Davis[37] noted both severe cardiac enlargement and congestive heart failure relieved by thyroid ingestion Numerous subsequent studies of the heart in myxedema have shown that enlargement of the heart occurs with regularity and that associated congestive heart failure is indeed a rarity [38 39]

Precise investigations by Blumgart and his associates[40] of the heart in myxedema developing after total thyroidectomy for the treatment of chronic heart disease have shown that in these patients as in those without underlying organic heart disease heart size regularly increases In this group of patients however changes in heart size were a resultant of opposing forces namely the dilatation caused by myxedema and the contraction in heart size resulting from recompensation of a failing heart Some patients with congestive failure from associated organic heart disease did not exhibit the usual dilatation because of improved heart function from the induced myxedema

The cause of the *enlarged heart* in myxedema has been ascribed to edema of the myocardium hypertrophy of heart muscle dilatation sec

ondary to a flabby musculature, and pericardial effusion The ready return to normal heart size following thyroid administration certainly excludes hypertrophy as a cause Kerr[1] has demonstrated by pericardial aspiration that pericardial effusion is a constant early and major factor in producing cardiac enlargement in myxedema

The *decreased amplitude of the heart beat* in myxedema is due to both pericardial effusion and reduction in the *cardiac output* which occurs regularly in myxedema The cardiac output may be lowered in proportion to the reduction in the rate of metabolism, in these circumstances heart failure will not result since the circulatory demand for oxygen does not exceed the capacity of the heart for delivery If the reduction of cardiac output is out of proportion to the decrease in oxygen consumption evidence of myocardial failure might appear

Concomitant with reduced cardiac output the velocity of blood flow in myxedema is greatly slowed[41] This slowing may be as great as that occurring in severe heart failure Similarly the reduction in cardiac output may reach the low levels of severe heart failure or shock In these circumstances the tissue requirements for oxygen are met by increasing the arteriovenous oxygen difference[42]

Changes in the electrocardiogram in myxedema are typical but not regular, as there may be no electrocardiographic changes in myxedema characteristic abnormalities include prolongation of the P R interval low amplitude of all complexes and flattening or inversion of the T waves Deep Q waves in leads 2 and 3 have been reported in juvenile myxedema[43] but we have not seen abnormal Q waves in adult myxedema except when there was associated coronary heart disease Thyroid administration slowly reverts the electrocardiogram to normal, the same effect occurs following removal of pericardial fluid

Although the *peripheral resistance* in the systemic circulation is increased with myxedema the *blood pressure* is unaffected probably owing to an absolute reduction in the cross sectional area of the peripheral vascular bed[44] With thyroid administration there is a return to normal levels of peripheral resistance

Cerebral blood flow and *renal blood flow* are greatly reduced in myxedema and are returned to normal by treatment with thyroid[45, 46]

Clinical Signs Symptoms and Course of Myxedema

Since idiopathic or spontaneous myxedema begins gradually it may not be recognized clinically until its features have become well estab

lished All the manifestations of myxedema may not become strikingly apparent for months or years The induction of myxedema by total thyroidectomy and by radioactive iodine has provided considerable knowledge regarding the development of the clinical picture of myxedema The complete syndrome of myxedema can develop in a matter of weeks if the removal or destruction of functioning thyroid tissue is complete The tardy development of the clinical picture in spontaneous myxedema therefore indicates a slow rate of destruction or atrophy of thyroid tissue

In the euthyroid patient total thyroidectomy produces early symptoms of hypothyroidism between the fourth and eighth week after operation these symptoms include cold extremities dry skin and decreased or absent sweating After the eighth week further signs and symptoms of myxedema develop puffiness of the face and extremities irritability fatigue stiffness of the extremities drowsiness tinnitus paresthesias and swelling of the tongue A similar course of events at a slower rate follows the induction of myxedema by radioactive iodine in euthyroid subjects[7 8]

The course of spontaneous myxedema is long and progressive the hypothyroid manifestations becoming more intense as the disease endures Untreated cases may survive for many years it is surprising how the disease may be overlooked even when fully established In the long standing case obesity is uncommon because the appetite is depressed far more than the metabolism the profound metabolic alterations eventually lead to anorexia lessened food intake and finally to actual wasting of body fat in the terminal stages Mental retardation may be so extreme as to cause admission to a mental hospital

While progression of symptomatology appears to be the rule in spontaneous or idiopathic myxedema it is not entirely certain that this is the case in hypothyroidism following extensive thyroidectomy for various lesions of the thyroid We have seen instances of this type of moderate hypothyroidism after radical subtotal thyroidectomy in which the manifestations of myxedema seemed stationary for several years at a clinically tolerable level In two such patients with carcinoma of the thyroid and partial hypothyroidism myxedema became complete in several weeks following the administration of a large dose of I^{131} When toxic diffuse goiter is treated by either subtotal thyroidectomy or radioactive iodine transient hypothyroidism not infrequently occurs The myxedemic symptoms are usually clear cut and may be so severe as to require thyroid

administration for a short period Nonetheless in such instances the capacity of the injured or residual thyroid tissue to recover and regenerate is readily demonstrated by the occurrence of spontaneous recovery May it not well be, therefore that myxedema can exist at several levels without inevitable downward progression? We think this is possible following surgery and after thiouracil therapy, and perhaps after I[131] therapy but probably not in spontaneous myxedema because in the last case the injury to the thyroid is more extensive and severe

The *symptoms and signs of myxedema* are due to deficiency of thyroid hormone rather than to hypometabolism and therefore cannot be correlated with the level of metabolism in the same manner as in thyrotoxicosis The most characteristic symptoms consist of the typical facies dryness and thickening of the skin and subcutaneous tissues a thickened and widened tongue a low-pitched and hoarse voice increased sensitivity to cold mental lethargy and physical torpor

The *facies* in myxedema is a composite of puffiness of the face and eyelids thickening of the nose and lips thinning of the eyebrows and a yellowish pallor with slight occasionally marked malar flush The swelling of the eyelids may be so marked as to reduce the palpebral fissure to a narrow slit The *skin* is generally dry rough thickened and cold it does not pit on pressure because of the characteristic mucinous infiltration Analogous changes are usually present in the *hair* and *nails,* the former is slow-growing dry and coarse the latter are thick and brittle

In the fully established case the *tongue* is mouth filling large and clumsy The *voice* is husky, low-pitched and rasping owing to edema of the vocal cords *Speech* is slow paced and articulation not entirely clear

A great *lethargy* settles early upon the myxedemic patient so that motion is slow and the sense of fatigue marked There is an increased desire to sleep both day and night

Marked *sensitivity to cold* with *decreased sweating* is an early regular, and typical symptom These patients prefer a warm environment and require extra covering in cold weather

Hypothyroidism decreases intestinal mobility with a resultant variety of functional disorders ranging from *constipation* to *megacolon* and *paralytic ileus*[17] *Anorexia* is common and undoubtedly explains the lack of marked obesity in a disease associated with the most profound depression of metabolism known to occur

Cardiovascular symptomatology is uncommon *Dyspnoea* may occur *Bradycardia* is the rule the *heart sounds* are decreased in intensity, *car-*

diac murmurs are absent unless there is associated heart disease The *blood pressure* is not altered by the disease When coronary artery disease is present *angina pectoris* may rarely occur in full blown myxedema or more often be precipitated as the hypothyroidism is brought under control with desiccated thyroid

Painful, crampy muscles and *joint pains* commonly occur as early symptoms of myxedema Alterations in the nervous system are profound *Memory loss paresthesias deafness, tinnitus vertigo,* and *awkwardness in locomotion* may all be present *Irritability* rather than *placidity* of temperament is not unusual *Psychotic-like* clinical syndromes and indeed true *psychoses* may occur Asher[48] has pointed out that the psychotic picture is varied delusions hallucinations paranoia dementia and depression may ensue Reversal of the psychotic state usually occurs with thyroid administration

Gonadal dysfunction may manifest itself by *menorrhagia, decreased libido, impotence* and *infertility* In women who become pregnant habitual abortion is common

Diagnosis and Differential Diagnosis

The diagnosis of myxedema is made on the basis of characteristic clinical and laboratory findings The *history* usually reveals that there has been increasing sensitivity to cold fatigue lethargy moderate weight gain memory failure dryness of the skin loss of hair anorexia and constipation A history of previous thyroidectomy or of treatment with radioactive iodine or the thiouracils is encountered in the post therapeutic types of myxedema The *examination* of the patient will reveal the classical facies of myxedema associated with a large tongue hoarseness of voice with slow speech a dry thickened and cold integument bradycardia supraclavicular fat pads coarse hair and brittle nails Rarely the clinical manifestations are not fully developed and the diagnosis must be more securely established by laboratory tests

The most dependable laboratory procedures comprise the *basal metabolism test* the estimation of the *serum protein bound iodine* and the measurement of the response to *radioactive iodine in tracer amounts* These three tests measure different functions of thyroid metabolism each subject to inherent error but almost infallible as a diagnostic triad

The *basal metabolism* is usually depressed to levels of minus 30 per cent or lower in satisfactory tests however it is similarly depressed in under-

nutrition schizophrenia Addison's disease, and occasionally in normal individuals Conversely, there are cases of myxedema particularly in patients with hypertension or heart disease, with only slight depression of the basal metabolism

The *protein-bound iodine* level of the serum measures the amount of circulating thyroid hormone and is ordinarily greatly depressed in myxedema to levels below 3 micrograms per 100 cc of blood However previous administration of iodine-containing dyes may produce normal or high values in myxedema contrariwise hypoproteinemia may depress the level of blood iodine in the absence of myxedema The level of protein-bound iodine is depressed for several weeks after the omission of thyroid administration to euthyroid subjects

The *uptake of radioactive iodine* is typically low in myxedema ranging from 6 to 13 per cent in our series of patients (Table VIII) Similarly depressed uptakes may be produced however, in both euthyroid and hyperthyroid patients by previous administration of stable iodine in any form In myxedema associated with goitrous enlargement or with chronic thyroiditis the uptake of I^{131} may be entirely normal

It is apparent therefore that only the most unusual circumstances would simultaneously lower metabolism depress the protein bound iodine level of the blood and reduce I^{131} uptake by the thyroid gland in a non myxedematous subject Ordinarily all three tests will provide satisfactory confirmation of the diagnosis, without the associated clinical syndrome however one would still be justified in a critical attitude toward the laboratory findings It is when the clinical picture is ambiguous especially in the patients with post-therapeutic myxedema that the full complement of laboratory tests is most useful, and often necessary The diagnosis of permanent myxedema carries with it the necessity of a lifetime of treatment with thyroid, it should therefore be confirmed adequately so that the patient can be impressed with the necessity of continuous thyroid treatment throughout the span of life This will prevent lapses of treatment with exposure to the mental and physical hazards of myxedema and at the same time will obviate unnecessary thyroid administration to euthyroid persons

The *differential diagnosis* of myxedema is restricted to a small number of diseases that resemble it superficially These include *syndromes associated with low metabolic rates chronic nephritis*, and *acromegaly* A low basal metabolism may be found in undernutrition schizophrenia Addison s disease and nephrosis Except for the non specific symptom of fatigue these states do not have the typical signs and symptoms of

myxedema and should present no real problem in differential diagnosis The patient with *chronic nephritis* may have a puffy pale face with a facies not dissimilar to that of myxedema However, the tongue is not enlarged the voice is not deepened nor is the skin thickened and dry Edema if present is of the pitting variety Albuminuria with hematuria and cylindruria are not found in uncomplicated myxedema The facies and widened tongue of *acromegaly* may suggest myxedema but the skin is normal warm and moist and there are marked bony enlargements as well as none of the soft tissue thickening found in myxedema

The most difficult disease to differentiate from idiopathic myxedema is myxedema secondary to hypopituitarism This type of myxedema has several features that differentiate it from idiopathic myxedema but there are many common features Clinically the facies may be myxedemic but the skin is atrophic alabaster and parchment like The tongue tends to be smaller than normal and the voice weakened and high pitched because of associated gonadal and adrenocortical failure Sexual hair is absent or scanty in pituitary myxedema to a more marked degree than in primary myxedema Amenorrhea is a constant feature of pituitary myxedema whereas excessive menstruation is characteristic of the primary type Roentgenograms of the skull in pituitary myxedema frequently reveal pituitary tumor except in the cases secondary to puerperal hemorrhage embolism trauma or small destructive lesions of the pituitary such as sarcoidosis tuberculosis or gumma The urinary excretion of 17 keto steroids is low in both types of myxedema but averages lower in the pituitary type because atrophy of the adrenal cortex and gonads is more marked in secondary myxedema Urinary gonadotrophins are high in primary myxedema and absent in pituitary myxedema Similarly thyrotrophin is usually elevated in primary myxedema and absent in pituitary myxedema The insulin tolerance test is normal in the former and markedly decreased in the latter instance Adrenal cortical function is significantly depressed in primary myxedema either directly or through the pituitary gland and its measurement is not a reliable method of differentiation [4, 5]

Querido and Stanbury [43] have attempted to differentiate the two types of myxedema by measuring the response to administered thyrotrophin of the basal metabolism the serum protein bound iodine and the I^{131} uptake but even these tests failed to separate the two diseases when there were even small remnants of functioning thyroid tissue

Prognosis

Untreated fully developed myxedema will eventuate in death after ten to fifteen years. Death occurs from cachexia or intercurrent infection with coma as the terminal manifestation. Death from untreated myxedema is undoubtedly a rarity; less rare is the disability occurring in patients who omit their thyroid medication. Such patients may remain undiagnosed for a considerable period if they do not return to the physician who first established the diagnosis of myxedema. For this reason patients should thoroughly understand the need for continued thyroid medication throughout the life span.

In myxedemic patients who are adequately and continuously treated with thyroid the prognosis is excellent. Murray[0] first treated a patient with myxedema by injections of an extract from a sheep's thyroid gland. The patient, a woman aged 46 with severe symptoms of myxedema, was maintained in excellent health by continuous administration of thyroid from 1891 until 19[illegible]0, when she died of intercurrent infection at the age of 74. Subsequently Raven[71] published the record of a patient with severe myxedema successfully treated with orally administered thyroid for 30 years, until death at the age of 94 (Fig. 64). The longest-treated case on record is that of Burgess,[5] whose patient took thyroid from 189[illegible] until her death in 1943 at the age of 9[illegible], a total of 52 years of continuous thyroid therapy.

Treatment

The aim of treatment in myxedema is the establishment of a euthyroid state except in those patients who may benefit from maintenance of a state of partial hypothyroidism because of associated heart disease or severe diabetes. In the vast majority of the cases treatment is best carried out with *desiccated thyroid*, as this is simple, efficacious and inexpensive. However, we have encountered several patients with spontaneous myxedema who responded inadequately to standard amounts of U.S.P. thyroid by mouth but did respond specifically to intravenously administered *thyroxine*. Apparently, malabsorption of desiccated thyroid from the gastro-intestinal tract was responsible for the substandard response. In all these instances oral thyroid in two to three times the usual dose was effective in relieving hypothyroid symptoms.

The official average dose of thyroid in the treatment of myxedema according to the United States Pharmacopeia is 60 mg. (1 gr.) daily.

USP thyroid contains not less than 0 17 per cent and not more than 0 23 per cent of iodine in thyroid combination In the treatment of myxedema the USP preparations are not only adequate but have the great advantage of relative constancy of composition since they must meet an accepted standard The *dosage* in any case should be individualized since the level of thyroid function established by a given dose will vary from patient to patient In addition something less than com



A B

Fig 64 A (1893) Mrs S age 65 bedridden Imbecile from myxedema of 20 years standing

Fig 64 B Mrs S after 5 weeks treatment with thyroid tablets The mental condition is as much improved as the bodily state

From Harington C R The thyroid gland its chemistry and physiology Oxford University Press London 1933

plete euthyroidism will be sought in many patients particularly those with coronary heart disease or congestive heart failure In coronary heart disease angina pectoris may be precipitated or become more severe as thyroid function approaches normal it is therefore of benefit to administer to such patients just enough thyroid to attain the most satisfactory balance between increasing angina and discomfort from the hypothyroid state A daily dose of 6 to 15 mg (1/10 to 1/4 gr) of thy-

roid is usually safe for the initiation of treatment in such cases This may be increased at weekly or biweekly intervals until the optimal dosage level is reached Thereafter, this dosage may be maintained or decreased should the anginal state worsen

In myxedematous patients with congestive heart failure the same cautious approach should be employed as in those with coronary heart disease However in patients with myxedema who do not have actual



Fig 64 C (1895) Mrs S after 15 months treatment with thyroid tablets The regrowth of the hair is a special feature

Fig 64 D (19 ,) Mrs S age 94 after nearly 30 years treatment Health normal Happy and mentally active

Died January 1924 Age over 94 Case reported again in Brit Med Jour., 4 October 1924

From Harington C R The thyroid gland its chemistry and physiology Oxford University Press London 1933

heart failure but who have a history of it one may proceed as in non cardiac patients to establish the level of treatment that is most compatible with the patient and his heart

Patients with uncomplicated myxedema ordinarily require from 1 0 to 180 mg (- to 3 gr) of U S P thyroid daily for the attainment of euthyroidism An initial dose of 60 mg (1 gr) is satisfactory for most

patients this amount will raise the basal metabolic rate from an average level of minus 40 per cent to an average level of minus 10 per cent by the end of 35 days However definite metabolic effects from this amount of thyroid will occur within several days Of these effects *diuresis* is the first to appear Subsequent to diuresis the *plasma volume rises* to normal and the *blood cholesterol decreases* to normal values Moderate *weight loss* ensues owing to loss of water and oxidation of protein

The improvement in the appearance of the patient is rapid because of early diuresis Intolerance to cold lethargy and speech abnormalities return quickly to normal in a matter of days to weeks The dryness of the skin and the increased sense of fatigue take much longer to improve and require adequate doses of thyroid to attain normality

At a dosage level of 180 mg (3 gr) daily of U S P thyroid the basal metabolism is raised more rapidly so that at the end of 0 days the metabolism will have risen from about minus 40 per cent to about minus 10 per cent

During the phase of metabolic adjustment to euthyroidism muscular pains arthralgias and palpitation may occur If there is *overdosage with thyroid* symptoms of mild hyperthyroidism will appear associated with an elevated basal metabolism Overdosage with thyroid in patients with myxedema however is perhaps no more readily attained than in the euthyroid subject we have seen little of it

In *pituitary myxedema* therapeusis is complicated by associated deficiency of the adrenal cortical and gonadal hormones Thyroid administration must be initiated cautiously and in small amounts to avoid precipitation of adrenal cortical failure Supplementary treatment with adrenal cortical hormones particularly cortisone and with gonadal hormones is essential When these hormones are administered with physiological effect the dosage of thyroid may be slowly raised to optimal levels These optimal levels vary to a greater extent from patient to patient than they do in patients with idiopathic myxedema as a rule they are considerably lower than in primary myxedema perhaps because only partial thyroid atrophy occurs in hypopituitarism [53]

In all types of myxedema there is greatly increased sensitivity to morphine and other respiratory depressants these drugs should be avoided

JUVENILE HYPOTHYROIDISM

Adult myxedema juvenile hypothyroidism and cretinism all repre

sent clinical states of severe thyroid hypofunction occurring at different age levels The differentiation of these clinical manifestations of hypo thyroidism is important because they may differ in etiology and do differ strikingly in prognosis Juvenile hypothyroidism represents post natal myxedema, whereas cretinism is a congenital anomaly that origi nates early in fetal development

The occurrence of hypothyroidism in children and adolescents causes a severe retardation in physical and mental growth and development which is most deleterious when it occurs in the very young and remains unrecognized The clinical and laboratory findings in juvenile hypo thyroidism are similar to those of adult myxedema However, the retarda tion of growth and development occurs, of course, only in juvenile hypothyroidism and cretinism

When hypothyroidism is acquired in infancy the clinical picture may closely resemble that of congenital hypothyroidism or cretinism If, how ever hypothyroidism develops later in childhood it differs from cretinism in many respects Somatic and mental development have had an initially normal stimulus before the onset of juvenile hypothyroidism, this period of postnatal euthyroidism is completely lacking in cretinism In juvenile hypothyroidism there is moderate retardation of growth but mental development may be normal although mental responses may be slowed as in adult myxedema Since osseous development is delayed the bone age will give a true indication of the time of onset of thyroid deficiency Since retardation of the bone age invariably occurs the diagnosis cannot be regarded as certainly established if this skeletal change is lacking Other types of dwarfism may cause delayed bony development and thus delayed epiphyseal ossification by itself is not pathognomonic of hypo thyroidism There is however a characteristic epiphyseal lesion in hypo thyroidism termed epiphyseal dysgenesis by Wilkins[54] This consists of pathological alterations in the cartilages of the epiphyses with irregu larities of ossification These appear as porous stippled, or fragmented osseous centers in the roentgenograms and resemble Legg Perthe s disease or osteochondritis deformans

Juvenile hypothyroidism is best treated with desiccated thyroid as in adult myxedema The dosage must be adequate to correct fully thyroid deficiency and to achieve normal growth and development Doses of 30 mg (½ gr) are safe initial amounts and they can be increased to the level required for complete euthyroidism and the attainment of a normal rate of osseous development The basal metabolism may be a

useful gauge in those children who are able to undergo this test Determination of bone age by roentgenograms at 6 month intervals is a reliable index to somatic development The serum protein bound iodine is a guide to adequacy of dosage and a useful indicator of overdosage

CRETINISM

Cretinism or congenital hypothyroidism represents a state of thyroid deficiency that has developed during early fetal life Most instances of childhood hypothyroidism are of this variety Clinically it occurs in two forms sporadic and endemic *Sporadic cretinism* occurs in nongoitrous areas and is usually associated with an atrophic or rudimentary thyroid Cases with large goiters in non endemic regions have been observed however and may be familial *Endemic cretinism* occurs in goitrous regions and is particularly common in areas of severe endemicity such as the Alps Carpathians and Himalayas Goiter is usually present in this variety of cretinism Goitrous parents with or without hypothyroidism in an endemic area tend to have cretinous offspring although these same may be born to normal parents living in an endemic region Ordinarily however goitrousness of several generations is required for the development of cretinism

The pathological changes in cretinism resemble those of myxedema with additional findings of delayed skeletal development epiphyseal dysgenesis and delayed formation of the tooth buds Changes in the central nervous system may occur particularly hypoplasia of the brain and enlargement of the anterior pituitary When goiter is present the pathological findings vary considerably showing hyperplasia involution atrophy and fibrosis We have observed one patient with sporadic cretinism and a large multinodular goiter which was intensely hyperplastic Following an extensive thyroidectomy the goiter recurred and the tissue removed at a second thyroidectomy showed both intense hyperplasia and undifferentiated carcinoma (Fig 65)

In *non goitrous cretinism* of the sporadic variety *the metabolism* of iodine resembles closely that observed in myxedema because the pathology of the two conditions is the same—that is there is actual or functional absence of the thyroid gland Therefore the uptake of radioactive iodine will be very low the level of protein bound iodine in the blood will approach zero and the degree of thyroid hypofunction will be severe[5] In the *goitrous cretin*, the situation is different because there is

thyroid tissue present that is capable of taking up radioactive iodine in amounts comparable to that seen in toxic diffuse goiter Some elaboration of thyroid hormone also occurs although in minimal amounts since the clinical picture may vary from mild to severe degrees of thyroid privation The marked avidity of the cretinous goiter for iodine is similar to that seen in the thiouracil induced goiter, the iodine has ready access to the gland but the thyroid cells are not capable of elaborating this iodine into the hormone in any appreciable amount This has been well demonstrated by Stanbury and Hedge [6] who found that while the goiter of cretinism readily accumulated radioactive iodine in large



Fig 65 Reproduced from Perlin D D and Gargill S L Trans Am Assoc Study Goiter 1947 51–62

A (L K) A 16-year old white girl with sporadic cretinism and a large multinodular goiter Moderate hyperplasia of thyroid with many small acini lined by relatively tall epithelium A few involuted acini also present (x157)

B (L K) Undifferentiated carcinoma of thyroid with attempted acinus formation Moderate anaplasia and marked hyperchromatism of cells Mitotic index moderately high (x157)

amounts this iodine was almost quantitatively discharged from the gland by thiocyanates indicating that it had not been organically bound

The *diagnosis of cretinism* is based upon clinical manifestations associated with characteristic laboratory and roentgenographic findings Classically cretinism manifests itself by dwarfism with an infantile habitus severe mental retardation physical lassitude grayish pallor of the skin macroglossia hypotonicity of the muscles coarsening and puffi-

ness of the face myxedematous thickening of the skin infantile naso-orbital configuration with a flat undeveloped nasal bridge retarded bony development and delayed dentition This advanced or complete state of cretinism occurs only with total athyreosis of long duration It is therefore not invariably present since many goitrous cretins do have some functioning thyroid tissue

According to Wilkins [54] the clinical manifestations of cretinism depend upon the age of onset of thyroid deficiency and the degree and duration of the deficiency The diagnosis is difficult during the first year of life because the characteristic physical and mental retardation may not be readily apparent With the passage of time the stasis in growth and development with retention of infantile body proportions becomes noticeable

The *differential diagnosis* from other types of dwarfism will be aided by appropriate laboratory and roentgenographic procedures The *serum cholesterol* may not be elevated until the cretin has reached the age of 1 or years but thereafter it is as frequently increased as in adult myxedema The concentration of *protein bound iodine* in the blood tends to approach zero and is a most useful test The *uptake of radioactive iodine* will be in the myxedema range in the non goitrous cretin but so variable in the goitrous type as to be useful only when depressed

Roentgenologic examination of the skeleton is particularly useful in the diagnosis of cretinism and its differentiation from other types of dwarfism Since appropriate epiphyseal development is never found in the untreated cretin the bone age lags considerably behind the chronological age of the patient In addition the roentgenogram will demonstrate epiphyseal dysgenesis a pathognomonic sign of cretinism

Hurxthal and Musulin [57] have observed several goitrous cretins in a non endemic area who were able to generate enough thyroid hormone to become euthyroid or even hyperthyroid This spontaneous production of thyroid hormone was associated with spurts in growth and development and elevation of the basal metabolism

The *treatment* of cretinism consists of the administration of enough thyroid to achieve euthyroidism and as normal somatic and mental development as can be attained The possibilities of achieving adequate physical growth are excellent and usually depend upon early recognition of the disease and prompt initiation of therapy Adequacy of mental development however is not secured even with the earliest possible treatment but a modest intellectual capacity is obtainable if treatment is started in early infancy The disposition of the untreated cretin is

pleasant and amiable Treatment initiated in late childhood or in adult life may lead to the development of a disagreeable and unmanageable personality without any compensating mental benefits It is therefore debatable whether the late-diagnosed cretin should receive more than enough thyroid to ameliorate the most troublesome symptoms of hyper thyroidism All other cases should be vigorously treated, however with doses of desiccated U S P thyroid ranging from 6 to 18 milligrams (1/10 to 3/10 gr) daily during the first year of life and from 60 to 180 milli grams (1 to 3 grains) daily thereafter The level of thyroid function may be determined by the rate of growth, skeletal development blood cholesterol and the protein-bound iodine of the blood

In goitrous cretins thyroidectomy should be performed if there are pressure symptoms or changes in the goiter suggesting malignancy

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PART IX

THYROIDITIS

I ACUTE THYROIDITIS

II SUBACUTE (Pseudotuberculous) THYROIDITIS

III CHRONIC THYROIDITIS

Inflammation of the thyroid gland is rare occurring in about 1 per cent of all patients with thyroid disease Its recognition is vital however since it may threaten the patient s life as in acute suppurative thyroiditis or interfere with respiration and swallowing as in chronic fibrosing thyroiditis of the Riedel type or depress thyroid function to myxedematous levels as in lymphadenoid goiter of the Hashimoto variety

Thyroiditis occurs as an acute inflammatory process either in previously normal thyroid glands or in those already goitrous In the latter instance the term *strumitis* has been employed Thyroiditis may also manifest itself in subacute and chronic forms

I ACUTE THYROIDITIS

Acute inflammatory disease of the thyroid gland may be suppurative or may be present as simple diffuse inflammation While a rare disease itself in the majority of cases it is associated with bacterial or viral disease elsewhere in the body and thus appears to be a blood borne infection Upper respiratory tract infections are frequent precursors in our experience but typhoid and paratyphoid fever dysentery pneumonia colon bacillus infections puerperal sepsis measles chickenpox and many other infectious diseases have been noted in association with acute thyroiditis

The *clinical course* is characterized by an acute onset with chills and moderate fever pain tenderness swelling and redness over the thyroid gland and leucocytosis Initially the process may be unilateral but eventually it involves the entire gland The pain may radiate to the ear jaws or shoulder it is usually aggravated by swallowing and extension of the neck Swelling and tenderness of the gland occur early and are marked

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In the *non suppurative cases* the disease runs a course of 5 or 6 days with gradual subsidence of the process without residual changes in the gland or alteration in its function in most patients In the *suppurative form*, fluctuation and softening of the gland appear as abscess formation occurs This may point toward the overlying skin or penetrate the trachea the pharynx the mediastinum or the adjacent cervical tissues Rupture into the mediastinum with mediastinitis is the most serious of these complications Perichondritis and necrosis of the trachea may occur from invasion of the trachea, pressure on the trachea may produce dyspnoea and cough, the recurrent laryngeal nerve may be involved occasionally there is edema of the larynx Dysphagia and stridor may be present when there is marked pressure on the esophagus and trachea

Recognition and early drainage are imperative in *the treatment of suppurative thyroiditis* because of these serious and occasionally fatal complications Antibiotics are undoubtedly indicated for acute thyroiditis whether suppurative or non suppurative especially if the organism of the associated infection is identified In our experience however, chemotherapy with antibiotics has not appeared of great value

II SUBACUTE (Pseudotuberculous) THYROIDITIS

Crile [1] has described a common form of non suppurative thyroiditis which clinically may resemble either acute or chronic thyroiditis It possesses however a distinctive pathology and Crile terms these cases subacute thyroiditis regardless of the clinical appearance Grossly there is usually diffuse involvement of a previously normal thyroid occasionally unilateral involvement may simulate nodules The thyroid is enlarged to 3 times its normal size and on cut section appears white and avascular and of turnip like consistency Histologically there is a granulomatous and fibrotic appearance with an increase in connective tissue a decrease in the size and number of the acini with disintegration of some of the acini The degenerating follicles contain cellular debris colloid histiocytes *and giant cells There is phagocytosis of the colloid by giant cells* in numerous focal areas which resemble tubercles but are without necrosis Infiltration with polymorphonuclear leucocytes lymphocytes plasma cells and histiocytes is widespread

Clinically subacute thyroiditis may present itself in an acute form with fever pain tenderness and the systemic symptoms of severe infection or in a chronic form with none of these signs or symptoms It should be emphasized that the pathology is identical in both forms Women are

much more commonly affected than men in a ratio of 10 to 1 The acute variety manifests itself by sore throat pain on swallowing and great tenderness over the thyroid gland There is radiation of the pain behind the ear on the affected side or to the head face or jaw Marked weakness and fever *ranging from 101° to 104° occur during the initial phase* of the disease slight fever may persist for several weeks occasionally months The history of a febrile onset can usually be elicited when the patient presents the chronic asymptomatic form of the disease Slight symptoms of tracheal pressure nervousness increased perspiration heat *intolerance and palpitation may also appear during the early phase of the* syndrome

On examination the thyroid gland appears very firm markedly tender and symmetrically enlarged Since in the chronic form the gland has a characteristic firmness but lacks the tenderness of the acute phase the diagnosis must be made by the characteristic history of acute onset with sore throat radiating pain to the ear or jaw pain on swallowing and neck tenderness

The sedimentation rate of the blood is always greatly increased in both the acute and chronic forms The uptake of radioactive iodine is ordinarily depressed to the myxedemic range in patients with bilateral involvement but the basal metabolism and the serum protein bound iodine *tend to be slightly elevated* [5] *The low uptake of I^{131} is probably due* to follicular cell damage and the increased amounts of circulating thyroid hormone to the escape of colloid into the circulation

Crile [1, 4] has established the diagnosis in doubtful cases by needle biopsy of the thyroid which has been accomplished without complications

Subacute thyroiditis has been well treated by roentgen irradiation in doses of about 800 r Osmond and Portmann [6] have utilized 200 kv filter equivalent to 1 0 mm half value layer copper 50 cm distance and 100 or 150 roentgens skin dose every other day for 4 to 6 treatments The portal size has been 10 by 10 cm or large enough to irradiate the entire gland

Irradiation results in rapid relief of pain and tenderness in several days with resolution of the process in 2 to 3 weeks Mild recurrences may be treated by a second course of roentgen therapy With subsidence of the disease thyroid function ordinarily returns to normal there is no tendency for progression into myxedema as in other forms of chronic thyroiditis

Antithyroidal drugs have been reported of value in the treatment of acute and subacute thyroiditis with rapid subsidence of the inflammatory

process[6,7] Cortisone has also been used in the treatment of subacute thyroiditis with marked beneficial effects[8,9] We ourselves have treated several cases with cortisone and have observed equally good results

Fig 66



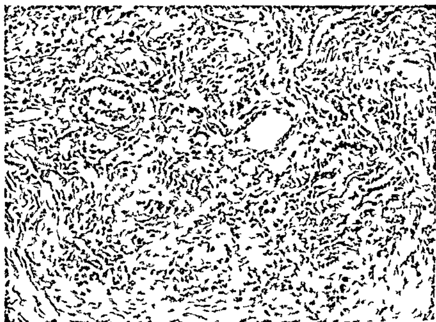
A *Chronic Thyroiditis—Struma lymphomatosa* Under this magnification the tissue looks more like a lymphnode than like a thyroid gland The basic though distorted lobular architecture of the thyroid gland however is readily discerned Clusters of small thyroid acini can be recognized about the lymphoid follicles Hematoxylin and eosin ×90

Fig 66



B *Chronic thyroiditis Hashimoto type* Diffuse lymphoid infiltration of the thyroid gland Several lymphoid follicles may be seen There is obvious destruction of thyroid parenchyma in the center of the field A few of the smaller acini are lined with cuboidal epithelium conspicuous by cell size and even eosinophilia of the cytoplasm (so-called Hurthle cell change) This gland showed no fibrosis Hematoxylin and eosin x90

Fig 66



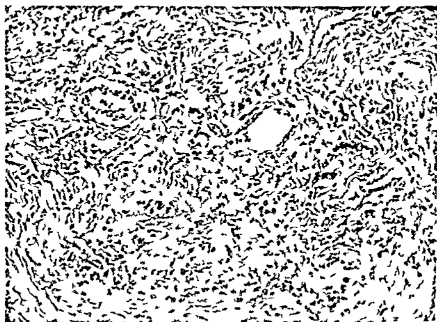
C *Chronic thyroiditis Riedel's type* A rare preserved thyroid follicle in a densely collagenized fibrous tissue background Scattered giant cells and a scant lymphocytic infiltration Hematoxylin and eosin ×90

Fig 66



D *Chronic thyroiditis Hashimoto type* Extensive substitution of the thyroid parenchyma by lymphoid tissue There are a number of well defined lymphoid follicles The remaining thyroid acini are spotted by their colloid contents staining prominently with MacCallum's periodic acid leukofuchsin routine x12

Fig 66



C *Chronic thyroiditis Riedel's type* A rare preserved thyroid follicle in a densely collagenized fibrous tissue background Scattered giant cells and a scant lymphocytic infiltration Hematoxylin and eosin ×90

a conservative thyroidectomy or lobectomy will often prove adequate[11] Operation hastens the development of myxedema and should therefore be minimal in extent In cases without pressure symptoms biopsy alone is adequate to establish the diagnosis and exclude carcinoma Roentgen ray therapy may then be utilized with benefit[13,14]

Riedel s Struma

Riedel s struma though rare is of clinical significance because of its resemblance to carcinoma and the production of severe pressure symptoms Pathologically the thyroid is involved in a severe sclerotic process which regularly spreads extrathyroidally to the surrounding structures and thus it may be regarded as a diffuse fibrosis of the neck with the thyroid at its center[14] The fibrotic process appears as a hypertrophic response to chronic inflammation This is evidenced by collections of monocytes lymphocytes and eosinophiles In addition pseudo giant cells may be present The lesion is extremely avascular and compresses the thyroid follicles Grossly the gland is white relatively dry free of lines of cleavage lacking normal lobulations and often attached through its capsule to the trachea and esophagus The process may be unilateral or bilateral in either case affecting the entire lobe of the involved side

Clinically about one third of patients with Riedel s struma are males and the age of the highest incidence in both males and females is somewhat younger than in Hashimoto s struma Severe pressure symptoms are common in Riedel s struma Involvement of the recurrent laryngeal nerve may produce hoarseness Tracheal and esophageal compression produce *dyspnea and dysphagia Hypothyroid symptoms however are less common* than in Hashimoto s struma because the disease is less often bilateral

The clinical examination of the thyroid in Riedel s struma usually shows the process to be localized in a part of the gland occasionally suggesting a hard nodule The mass is extremely hard and ligneous in consistency with fixation to surrounding tissues Compression and deviation of the trachea and occasionally vocal cord paralysis may be manifest The clinical resemblance to invasive carcinoma is so striking that operation is necessary for diagnosis as well as for relief of obstructive symptoms Myxedema is rarely present when the patient first appears on the clinical scene

The treatment of Riedel s struma by thyroidectomy is difficult and hazardous because of the extensive fibrosis Damage to the trachea carotid

III CHRONIC THYROIDITIS

Chronic thyroiditis is better defined pathologically than clinically As a pathologic entity it occurs in two distinct and probably unrelated forms namely Hashimoto s struma [10] (struma lymphomatosa lymphadenoid goiter) and Riedel s struma [11] (chronic fibrous or ligneous thyroiditis) In addition specific forms of chronic thyroiditis such as tuberculous syphilitic actinomycotic et cetera have been described These are extremely rare and we ourselves have never seen any

Hashimoto s Struma

Hashimoto s struma is characterized pathologically by marked infiltration with lymphoid cells and the formation of secondary lymph follicles *This reaction in itself is not diagnostic of the disease, since a similar picture may be seen in diffuse toxic goiter* [10, 1] Struma lymphomatosa however exhibits in addition extensive acidophilic degeneration of the epithelial cells of the thyroid with replacement of functioning thyroid tissue by lymphoid and fibrous tissue This pathological change is almost always spread diffusely and rather symmetrically throughout the entire gland involving both lobes and the isthmus Grossly, the gland appears pale gray is firm but has not the woody or ligneous consistency that is seen in Riedel s struma Extrathyroidal extension of the process is rare

Clinically, Hashimoto's struma is most often seen in women past middle age Aside from the presence of goiter complaints are infrequent Because of the diffuse and progressive nature of the disease the eventual development of myxedema is frequent In some instances pressure symptoms may occur from constriction of the trachea These are mainly dyspnea cough hoarseness and dysphagia

The clinical diagnosis of Hashimoto s struma is difficult The onset of the disease is gradual and unattended with pain or fever On examination the thyroid is bilaterally enlarged to 2 or 4 times normal size very firm in consistency with sharp outlines of the normal anatomy of the gland The surface appears rubbery and lobulated occasionally a distinct nodule appears palpable but this is rarely confirmed at operation [13, 14, 15]

If the diagnosis of chronic thyroiditis of the Hashimoto type could be made without biopsy little in the way of treatment would be necessary except for the administration of desiccated thyroid to those patients with hypothyroidism For the cases with marked pressure symptoms, however,

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sheath and recurrent laryngeal nerves may occur with too radical operation Crile[14] feels that a degenerating adenoma is at the center of the fibrosed lobe in most cases and that removal of this central core will cause arrest of the process Marshall and his associates[1] advise excision of the isthmus as adequate surgery in most instances for relief of pressure symptoms Joll[16] has carried out removal of as much thyroid tissue as is possible without damage to surrounding structures The surgery in all instances will be rendered safer if the surgeon apprises himself by early biopsy of the nature of the lesion and does not mistakenly attempt radical excision of nonexistent carcinoma Post-operatively myxedema may be anticipated in many instances and should be appropriately treated with desiccated thyroid

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PART X

BENIGN AND MALIGNANT NEOPLASMS OF THE THYROID

The clinical and pathological differentiation between benign and malignant neoplasms of the thyroid is beset with difficulties that rarely occur with tumors of other organs These difficulties are threefold first the clinical criteria of malignancy may be absent or misleading in the majority of thyroid cancers second there is great disparity between the histological appearance of the neoplasm and its biological behavior third the distinction between hyperplasia and neoplasia is nowhere more difficult than in the thyroid gland In spite of these difficulties a consensus of opinion with regard to the pathology incidence and treatment of thyroid neoplasms has emerged as a result of studies from many clinics including our own

Benign Neoplasms

Benign neoplasms of the thyroid consist of true adenomas in the pathological sense and are difficult to separate from the large group of thyroid nodules of an involutional or colloid nature These latter represent the end result of the processes of hyperplasia and involution of the Marine cycle whereas the adenoma represents a true epithelial neoplasm It is homogeneous completely encapsulated or sharply distinguished from surrounding thyroid tissue which it usually compresses In addition an adenoma has the features of benignity namely the absence of invasiveness or metastases or both Mitoses and pleomorphism cannot be used as criteria of malignancy with the same specificity as in non thyroid tumors since they may occur in the hyperplastic thyroid

The characteristics of benign neoplasms—namely *homogeneity*, *encapsulation*, *distinction from adjacent tissue*, *compression of surrounding cells* and *benign biological behavior*—are also applicable to many involutional nodules of the thyroid However the *papilliferrous tumors* are morphologically analogous to papilliferrous adenomas in other organs

considered malignant and classified as malignant papillary cystadenomas or papillary adenocarcinoma.

The confusion about the pathological status of the simple or nonpapillary adenomas of the thyroid gland is further increased by the fact that a small group of apparently benign adenomas do metastasize by way of the blood stream to other tissues, especially to the bones and lungs. The only clue to the malignant nature of these tumors may be their invasion of one or more veins; histologically they appear as embryonal or *fetal adenomas*.

Hurthle cell adenomas are usually benign, exhibiting slow growth, encapsulation, and failure to recur after removal; occasionally, however, they may be malignant. These tumors probably arise from the ordinary thyroid epithelium; microscopically they consist of large eosinophilic finely granular or foamy polygonal cells arranged in solid trabeculae or in small acini. Friedman[4] has demonstrated that Hurthle cells develop not only in thyroid hyperplasia, Hashimoto's struma, and exhaustion atrophy but also as a result of thyroid irradiation, thiouracil administration, and partial thyroidectomy.

The *papillary tumors of the thyroid* are regarded by pathologists as true tumors, as distinguished from the usual more controversial benign adenomas. Willis,[5] however, regards them all as malignant tumors and states that "papillary adenomas cannot be distinguished from papillary carcinomas . . . however highly organized and quiescent in appearance."

Dobyns and Lennon[6] have studied the functional behavior of benign thyroid tumors by means of radio-autography. Their adenomas included all encapsulated discrete tissue masses differing histologically from the surrounding thyroid tissue. The degree of uptake of radioactive iodine as measured by radio-autography was utilized as a test of thyroid function, since the degree of collection of radioactive iodine represents the degree of function of the thyroid tissue. They found a general parallel relationship between differentiation and function, the most embryonic tumors having least function as compared with a high functional capacity in the more differentiated tumors. It was also noted that hyperplastic adenomas occurred both with and without hyperfunction, and that those with hyperfunction tended to suppress activity of otherwise normal thyroid tissue. The hyperfunctioning adenomas occurred with or without clinical *hyperthyroidism*.

On the basis of their studies, Dobyns and Lennon[6] suggest the following spectrum of increasing differentiation of thyroid adenomas: (1) solid cellular fetal adenoma or embryonal adenoma, (2) adenomas with solid

and are therefore more readily classified as true adenomas by the pathologist The papilliferrous adenoma or papillary cystadenoma consists of cuboidal or columnar cells arranged on stalk-like structures of fibrous tissue with a vascular core, the whole structure represents hyperplasia of the epithelial lining of a cystic adenoma

Other types of benign adenomas are less characteristic structurally and merge indistinguishably with involutional nodules of a colloid or fetal type Zimmerman and his associates[1] have classified all varieties of non papilliferrous benign tumors of the thyroid as simple adenomas They include all tumors made up of cords of eosinophilic cells which are regular in size and shape or masses of very small acinar structures which are devoid of colloid

Wegelin has offered a more elaborate classification of benign adenomas consisting of the following (1) *trabecular adenoma*, resembling embryonal fetal thyroid and showing cords of cells packed closely together (2) *tubular adenoma*, resembling more differentiated fetal thyroid and showing cords of cells less densely packed and arranged in tubular form, (3) *microfollicular adenoma*, resembling a still later stage of fetal thyroid and made up of closely packed small, round follicles of cuboidal cells essentially without colloid (4) *micro and macrofollicular adenoma* showing both small follicles with cuboidal epithelium and large follicles lined with cuboidal epithelium and containing colloid with interacinous material of a hyaline fibrous or structureless nature, (5) *macrofollicular adenoma*, showing large colloid follicles lined by flat epithelium (6) *Hurthle cell adenoma*, (7) *papillary cystadenoma*, and (8) *hyperplastic adenoma*

Warren[3] includes the great bulk of thyroid nodules under the classification of adenoma and recognizes the following five types (1) the *embryonal adenoma*, in which masses and strands of poorly differentiated thyroid cells traverse a rather gelatinous stroma, (2) the *fetal adenoma* in which poorly developed follicles occur usually imbedded in a rather abundant gelatinous stroma (3) the *simple adenoma*, which may closely resemble the histologic picture of the normal thyroid gland (4) the *colloid adenoma* in which extensive storage of colloid occurs in greatly distended follicles, and (5) the *Hurthle cell adenoma*, characterized by large polyhedral cells with rather strikingly clear cytoplasm Warren separates the papillary tumors from the foregoing group of adenomas and considers those papillary cystadenomas as benign which do not show invasiveness or metastases, all other papillary tumors are

considered malignant and classified as malignant papillary cystadenomas or papillary adenocarcinoma

The confusion about the pathological status of the simple or non papillary adenomas of the thyroid gland is further increased by the fact that a small group of apparently benign adenomas do metastasize by way of the blood stream to other tissues especially to the bones and lungs The only clue to the malignant nature of these tumors may be their invasion of one or more veins histologically they appear as embryonal or fetal adenomas

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On the basis of their studies Dobyns and Lennon[6] suggest the following spectrum of increasing differentiation of thyroid adenomas (1) solid cellular fetal adenoma or embryonal adenoma ( ) adenomas with solid

strands of cells and very primitive acini, (3) adenomas with minute acini, (4) hyperplastic adenomas with large and small acini, (5) mixed large and small acini with colloid, (6) adenoma with large acini or colloid adenoma Colloid formation appears to be a sign of maturity and differentiation and tends to be associated with increased iodine avidity, there are many exceptions, however, to this relationship

Malignant Neoplasms

Malignant neoplasms of the thyroid may be benign in appearance and malignant in behavior conversely, they may appear quite malignant but metastasize or grow so slowly that a partially benign clinical course ensues or finally, an identical neoplastic pathology may be associated with either a benign or malignant clinical course It is the dichotomy between behavior and appearance as well as the slow clinical progression of many thyroid carcinomas which has made the subject so difficult to clarify A study of the natural history of thyroid cancer indicates that follow-up periods of 5 to 25 years are essential in order to appreciate the nature of many thyroid cancers which grow slowly metastasize late and are prone to recur tardily after removal

The classification of thyroid malignancy described by Lahey, Hare and Warren[7] arranges cancers of the thyroid in an ascending scale of malignancy as follows

I *Low malignancy*
  A *Angio invasive tumors*
    1 adenoma
    2 malignant papillary cystadenoma
II *Moderate malignancy*
  A *Adenocarcinoma*
    1 papillary
    2 alveolar or solid
    3 Hurthle cell
III *High malignancy*
  A *Carcinoma*
    1 small cell (carcinoma simplex)
    2 giant cell
    3 epidermoid
  B *Sarcoma*
    1 fibrosarcoma
    2 lymphosarcoma

Carcinomas of the thyroid may be more simply divided into two main groups the *papillary* and the *non papillary* [8] This classification is clinically useful since it indicates the route of metastasis papillary carcinomas are generally transmitted through the lymphatics to regional lymph nodes whereas non papillary carcinomas are angio invasive metastasizing through the blood stream The path of metastasis has an important influence upon the clinical behavior and prognosis of these tumors and must be considered in their treatment Papillary carcinomas are usually of low to moderate malignancy whereas the non papillary tumors vary in malignancy from the low grade angio invasive adenoma to the very malignant small cell undifferentiated carcinoma

The *angio invasive adenomas* represent those neoplasms of the thyroid with the histology of benign adenomas which in addition show both blood vessel invasion and clinical malignancy as manifested by capsular invasion and metastases to regional lymph nodes or other organs These tumors may be either papillary cystadenomas or non papillary adenomas The malignant behavior of these tumors was first explained by Graham [9] who demonstrated their capacity to invade adjacent blood vessels and thus spread to other tissues While they are of a low order of malignancy in their rate of growth blood borne metastases to the lungs or bones may occur early Of the non papillary adenomas *embryonal* and *fetal adenomas* are the commonest to show blood vessel invasion The interpretation of blood vessel invasion requires care in the elimination of artifacts Warren [11] requires actual invasion of the vessel wall by tumor or adherence of tumor tissue to the wall In his study of 1114 excised adenomas blood vessel invasion occurred in less than 3 per cent only 10 per cent of the adenomas with blood vessel invasion metastasized or recurred locally after removal Thus 0 3 per cent of apparently benign adenomas will show blood vessel invasion associated with malignant behavior Warren [11] has buttressed the malignant connotation of blood vessel invasion by demonstrating that 1080 patients having adenomas without blood vessel invasion did not develop malignancy during a follow up period of 2½ to 7 years after operation A longer follow up period would of course be desirable to establish the complete benignity of these adenomas

Angio invasive adenomas are generally encapsulated and are of low-grade malignancy They metastasize through the blood stream but at least half the cases show regional lymph node involvement Carcinomatous tissue in the neck veins may occasionally be demonstrated at operation Invasion of the capsule with fixation occurs late so that the

true nature of these tumors may not be appreciated until a distant blood borne metastasis has appeared The metastases of these adenomas vary considerably in histology from the primary tumor, some may be un differentiated but others appear so much like normal thyroid that they have been termed benign metastasizing goiter' since Cohnheim s original description [11] Wegelin [1] has discussed the angio-invasive adenoma its differentiation from benign adenomas, and its metastatic proclivities as follows I agree entirely with Graham s statement that malignant and benign adenomas show no difference as to the character of the cells the mitoses the colloid content or the structure of the follicles Yet the metastasizing adenoma must possess greater growth activity This is shown histologically, solely by invasion of the blood vessels and when one examines serial sections of such nodules one can nearly always find tumor tissue in a vein of the capsule That is we have here a neoplasm which is highly differentiated and of typical structure, and which betrays its malignancy only in its relations to the blood vessels The metastases may also show a typical structure, they may indeed store up iodine containing colloid and like the benign adenomas, develop the characteristic thyroid gland action upon tadpoles, as was shown by my pupil C Abelin That the functional effects of such metastases can replace those of the normal thyroid gland is shown in a remarkable case described by von Eiselsberg'

The capacity of metastases from thyroid cancer to secrete thyroid hormone and carry on thyroid function was thus appreciated as early as 1894 by von Eiselsberg [13] The metastases of angio invasive adenomas are commonest in the bones and the skeletal metastases may be the first indication of the thyroid malignancy, especially when the primary adenoma is small or impalpable The growth of bony metastases may be so slow that patients will survive for many years after their appearance

Frazell and Foote [14] as well as Dobyns and Maloof [15] classify the non papillary, angio-invasive adenomas as *follicular carcinomas* This is a useful descriptive term since it indicates clearly the presence of colloid containing follicles as the primary element in the tumor

Papillary cystadenomas of the thyroid may be either benign or malig nant When benign the tumor is encapsulated and histologically appears as hyperplasia of the lining epithelium of a cystic adenoma However benign in appearance, these tumors must be adjudged malignant when there is capsular or blood vessel invasion or metastases to regional lymph nodes Because of their low-grade malignant potential a follow up period of many years is essential to demonstrate the cancerous nature of some of

these tumors Their papillary structure justifiably causes pathologists to hesitate in classifying even the most benign appearing ones as non malignant The tissue selected for microscopic study may be from an area without capsular or blood vessel invasion which is in fact present in some other area the diagnosis may be considered benign until a later recurrence calls attention to the real nature of the primary tumor

Thyroid tumors of moderate malignancy comprise the papillary alveolar and Hurthle cell adenocarcinomas The *papillary adeno carcinomas* constitute more than 50 per cent of all thyroid malignancy The transition from papillary cystadenoma to papillary adenocarcinoma is marked by increased anaplasia and loss of encapsulation Pathologically these tumors are epithelial neoplasms partly or wholly arranged in papillae In the pure forms there is little tendency to acinar formation Histological variations from the pure papillary form occur and in these variants there may be significant formation of acini containing colloid thus a papillary adenocarcinoma may be predominantly papillary and yet contain enough follicular elements materially to enhance the uptake of radioactive iodine

Characteristically papillary adenocarcinomas are non encapsulated and tend to invade surrounding normal thyroid they are therefore not enucleable as such Their degree of malignancy is low in that growth is retarded and metastases occur late Lymphatic spread to adjacent nodes is common but metastases to the lungs or to bones are not rare These metastases in turn show a remarkably slow rate of growth and patients have survived for years with pulmonary or osseous metastases

Papillary adenocarcinoma is frequently found in nodules measuring 1 cm or less in diameter thus the first manifestation of the cancer may be found in nearby lymph nodes or in the region of the neck lateral to the thyroid Black [18] has re emphasized that so called *lateral aberrant thyroid tumors are invariably metastatic from a primary papillary adenocar* cinoma of the corresponding lobe of the thyroid The primary tumor may be microscopic or measure only a few millimeters in diameter and therefore require serial sections for its identification In several instances we have encountered metastases to the cervical nodes which arose from a primary lesion in the contralateral lobe of the thyroid with no involvement of the thyroid lobe on the same side as the cervical metastasis

Papillary adenocarcinoma is occasionally associated with exophthalmic goiter Black [18] has found incidental papillary adenocarcinoma in 11 patients with exophthalmic goiter among a total series of 112 cases of

papillary adenocarcinoma — an incidence of about 10 per cent Regional lymph node involvement was absent in all these cases

Papillary adenocarcinoma is the characteristic malignancy of the thyroid gland in childhood and youth

The second type of adenocarcinomas includes *the alveolar and solid adenocarcinomas* Some authors classify follicular adenocarcinomas in *this group* also *rather than in the less malignant group of angio invasive* adenomas from which they may be histologically indistinguishable in many sections The alveolar carcinoma may be structurally differentiated to the point of lumen formation or may be entirely solid from cellular proliferation and without a lumen Colloid formation is absent or extremely rare in most of these tumors but in a small percentage there are colloid containing follicles so that one may classify these tumors as follicular and alveolar adenocarcinomas The follicular and alveolar adenocarcinomas tend to be encapsulated for a time but are moderately malignant because of spread by the blood stream

The solid alveolar adenocarcinomas are more malignant since they are unencapsulated and tend to spread throughout the thyroid gland and to infiltrate surrounding tissues Histologically they show heterogeneity and variability within the same tumor They are made up of masses and strands of undifferentiated epithelial cells with little tendency to follicle formation or papillation Clinically they appear as hard fixed, invasive tumors with prominent obstructive symptoms Metastases to regional lymph nodes and through the blood stream to lungs and bones are common

Benign metastasizing goiter has already been discussed under the angio-invasive adenoma Some authors prefer, however to classify these tumors under the more malignant group of follicular and alveolar adenocarcinomas Their histology in general, reproduces the structure of normal thyroid follicles but careful study by multiple sections of primary and metastatic lesions will frequently disclose the morphologic picture of alveolar adenocarcinoma

The *Hurthle cell adenocarcinoma* is rare in occurrence Histologically it resembles the Hurthle cell adenoma but shows in addition an irregular arrangement of cells with invasion of adjacent thyroid tissue Clinically, these tumors tend to be unilateral and encapsulated Chesky Dreese and Hellwig [17] and Frazell and Foote [14] have studied 25 and 27 instances of Hurthle cell tumor respectively Their conclusions are quite opposite The former group found these tumors of a low order of malignancy as regards tendency to metastasize or to capsular invasion, even though

many showed blood vessel invasion Follow up periods ranged between 1½ and 9 years Chesky and his associates advised lobectomy without neck dissection as adequate treatment Frazell and Foote however felt that Hurthle cell tumors with a disorderly microscopic structure were quite malignant in behavior whereas those with an orderly architecture were benign or only sporadically malignant In this tumor as with other tumors of the thyroid microscopic structure belies biological behavior

The highly malignant tumors of the thyroid comprise the *small cell giant cell* and *epidermoid* types of carcinoma and the *sarcomas* consisting of the *fibrosarcomas* and *lymphosarcomas*

Small cell carcinoma, or *carcinoma simplex* occurs as solid masses or cords of small deeply staining anaplastic cells with frequent mitoses This tumor is highly invasive The histological picture may resemble thyroiditis of the Hashimoto type or lymphoma but the presence of local invasiveness indicates its true nature

Giant cell carcinomas are extremely malignant tumors composed of large bizarre cells with irregular mitoses They tend to occur in women over the age of 50 and grow with such rapidity as to produce death by local invasion before distant metastases can occur Clinically they are large and bulky with a soft meaty consistency

Epidermoid or squamous cell carcinomas are extremely rare and appear to arise either from remnants of the thyroglossal duct or by metaplasia of thyroid epithelium [18]

Fibrosarcomas of the thyroid are also extremely rare We have seen none in our clinic Pathologically the cells form fibroglia and collagen fibrils and by these criteria can be differentiated from giant cell carcinomas

Primary *lymphosarcoma of the thyroid* is infrequent Dinsmore Dempsey and Hazard have reported 8 cases [19] Histologically it may be confused with either small cell carcinoma or thyroiditis of the Hashimoto type The differentiation from the latter is again facilitated by the invasiveness of lymphosarcoma as compared with the capsular containment of thyroiditis

Metastatic or Exogenous Tumors in the Thyroid

The thyroid gland is occasionally the site of metastases originating from malignancy in other organs Mayo and Schlicke [9] reported 19 such instances in their experience and pointed out that metastatic lesions in the

papillary adenocarcinoma — an incidence of about 10 per cent Regional lymph node involvement was absent in all these cases

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features requisite for the diagnosis of malignancy — that is local recurrence and fatal issue with inadequate removal

In nodular goiter associated with thyrotoxicosis the incidence of carcinoma may be as low as 1 per cent except in the Hurthle cell tumors where as many as 36 per cent were associated with hyperthyroidism in one series[17]

A high incidence of cancer in thyroid nodules is common in children Pemberton and Black[6] found 18 carcinomas of the thyroid in 53 children under the age of 15 who had thyroidectomies for non toxic nodular goiter Duffy and Fitzgerald[7] in a study of cancer of the thyroid in children found that about one half were papillary adeno carcinomas and an additional one third were alveolar and follicular adenocarcinomas This distribution of papillary adenocarcinoma in children is in accord with that found in thyroid cancer in the adult but the alveolar and follicular forms were three times as common as in adults While both papillary and alveolar adenocarcinomas behaved like tumors of low grade malignancy in the rate of growth of the primary tumor or metastases a considerable number had metastases to the lungs and almost all had metastases to the cervical lymph nodes

The etiological relationship between pre existing benign nodules and the development of thyroid cancer is difficult to establish in spite of the incidence of malignancy in surgically removed thyroid nodules Does the non neoplastic nodule change its growth potential and become malignant or is the carcinomatous nodule malignant from the beginning Many malignant tumors of the thyroid undoubtedly remain small for long periods The mere fact that a tumor of the thyroid has been present for a long time does not therefore indicate that it was benign initially The higher incidence of cancer in solitary nodules is some indication that carcinoma is present from the beginning rather than arising as degeneration of previously benign nodules If the latter were true the higher incidence would occur in multinodular goiters since there are more nodules in a given number of patients

Experimentally there is evidence that the process of hyperplasia which gives rise to non neoplastic nodules and adenomas may be a factor in the development of malignancy The experimental and clinical use of thiourea derivatives has provided significant information in this regard In thiouracil induced goiters there occurs marked cellular hyperplasia with numerous mitoses Bielschowsky[8] induced benign and malignant tumors in the thyroid glands of rats fed simultaneously with the carcinogenic agent 2 acetyl amino fluorine and allyl thiourea Purves and Gries-

thyroid have arisen from tumors in almost every organ of the body We have seen one instance of metastasis to the thyroid from a bronchogenic carcinoma and several from hypernephroma Embolic tumor cells have been found in 11 per cent of thyroid glands of patients dying of carcinoma arising in other organs in a small series carefully examined by Rice [1] Clinically the diagnosis of metastatic tumor may be suspected when there is a sudden increase in the size of thyroid in patients with known malignancy elsewhere in the body Similarly thyroidectomy for nodular goiter has occasionally revealed the existence of unsuspected malignancy which has metastasized to the thyroid from another organ

Relation of Carcinoma of the Thyroid to Nodular Goiter

The relation of carcinoma of the thyroid to nodular goiter has become increasingly clarified through analyses of large series of patients with nodular goiter treated by thyroidectomy The subject has been well reviewed by Cole and his associates [3] and by Cope and his co workers [4] We have analyzed our own experience in the treatment of 200 cases of nodular goiter [5] In patients with non-toxic nodular goiter the incidence of carcinoma of the thyroid is surprisingly high varying from 10 per cent in Cope s series to 17 2 per cent in Cole s series In our material malignancy occurred in 12 5 per cent of all patients with nodular goiter Further analysis of all this material indicates that solitary nodules are more likely to be carcinomatous than multiple nodules Thus Cole found 4 4 per cent of solitary non toxic nodules to contain carcinoma, whereas Cope encountered carcinoma in 19 per cent of a similar group and we found 14 4 per cent of solitary nodules to be carcinomatous

Multinodular goiters are less likely to be malignant, the incidence of carcinoma ranging from 7 to 10 per cent in most series This however, amounts to a considerable incidence of carcinoma Clinically it is not always possible accurately to distinguish solitary from multiple nodules thus in our experience many goiters with presumably single nodules proved to be multinodular on pathologic examination and a few diffusely enlarged glands were found to contain unsuspected nodules

The diagnosis of malignancy of the thyroid in the series reported by Cole Cope and ourselves was not exclusively based on histopathological appearance but in most instances rested upon such conclusive evidence of malignant behavior as capsular invasion, local spread lymph gland or distant metastases Adequate follow-up showed furthermore the other

thyroid therefore comprises both these activities Radioactive iodine has been especially useful for the measurement of iodine accumulation the estimation of hormone synthesis requires either precise chemical analysis of thyroid tissue or the usual indices of thyroid function namely the basal metabolism and the protein bound iodine of the blood

The uptake of radioactive iodine by thyroid neoplasms has been studied both by radio autography and by external counting utilizing directional methods Radio autography is a sensitive method of measuring iodine concentration and when laid over histological sections enables a precise microscopic localization of the uptake as well as its intensity

The function of various types of thyroid carcinomas as revealed by radio autography after the administration of radioactive iodine has been carefully studied by Fitzgerald and Foote[35] in 100 specimens from 86 patients Since normally the thyroid shows considerable variability in its concentration of radioactive iodine adjacent follicles may accumulate much to little or none of the isotope When there is uptake the radio activity is confined to the colloid The investigations of Marinelli[3] and Seidlin[37] had demonstrated a considerable degree of correlation between the histologic structure of thyroid carcinoma and I^{131} uptake the more differentiated tumors took up iodine more regularly than the less differentiated Marinelli[38] noted two determining factors in I^{131} accumulation (1) an orderly cell arrangement in a follicular pattern and (2) the presence of colloid like material Thus all the benign metastasizing goiters in his series concentrated radioactive iodine and most of the adenocarcinomas containing follicular areas also accumulated I^{131}

Fitzgerald and Foote[3] found that papillary adenocarcinomas took up little or no I^{131} when they were histologically of a fairly pure type—that is predominantly papilliferous with little true gland and colloid formation When the papillary adenocarcinoma was of a mixed type with areas of alveolar or follicle formation with colloid or with both the likelihood of I^{131} retention was greatly increased The follicular and alveolar carcinomas while more malignant than the papillary group are histologically more differentiated in that their structure resembles normal thyroid epithelium The majority of these tumors will take up appreciable amounts of radioactive iodine in proportion to the quantity of colloid present Alveolar areas without follicle formation will not usually behave in this manner In addition within the tumor as in the normal gland there is marked variation in isotope concentration

The solid adenocarcinomas as a group did not accumulate I^{131} but those that contained various admixtures of alveolar follicular or papillary

bach[9,30] demonstrated that prolonged hyperplasia of the thyroid produced by allyl thiourea led to the development of thyroid adenomas, rats maintained for long periods on thiourea itself developed carcinomatous thyroid nodules which metastasized to the lungs Money and Rawson[31] produced non-metastasizing adenomas in the thyroid of rats treated for long periods with thiouracil alone The histological picture produced varied greatly and presented nearly all the types of benign tumors found in the human thyroid gland Morris, Dalton, and Green[3] by means of progressive transplants of mouse thyroid glands made hyperplastic with thiouracil were eventually able to produce autonomous thyroid neoplasms which frequently developed pulmonary metastases They postulated that prolonged thyrotrophin stimulation brought about the transformation of hyperplasia to neoplasia and concluded that they had produced neoplastic, potentially malignant tissue by prolonged thyrotrophin stimulation

The demonstration by Greene and his associates[33] that human malignant tumors survived and grew after transplantation into the anterior chamber of the guinea pig's eye, whereas benign tumors and normal adult tissues were absorbed led Dobyns and Lennon[34] to study the growth and histologic changes of human thyroidal tumors similarly transplanted Numerous malignant lesions survived and grew, however, normal thyroid tissue occasionally also survived The fact that two histologically benign but primitive fetal adenomas both survived and grew upon transplantation suggests that they were biologically malignant or at least had a high growth potential Carcinomas of the thyroid after numerous transplants tended to become more differentiated and one anaplastic carcinoma evolved many histologic patterns This new approach to the study of thyroid tumors indicates their potential with regard to differentiation and explains, in part, the considerable difficulty besetting the pathologist when he attempts to predict benignity from structure alone

Functional Behavior of Malignant Neoplasms of the Thyroid

The function of the thyroid cell is the elaboration of thyroid hormone In order to accomplish this purpose it has a specialized ability to take up iodine The thyroid cell therefore has its primary function of hormone synthesis closely linked to its secondary function of iodine collection The functional behavior of malignant neoplasms of the

strated that total removal of the thyroid by surgery or radioactive iodine was efficacious in inducing uptake in metastases from thyroid cancer He ascribed this effect to (1) increased thyrotrophin from the induced myxedema and (2) the absence of the thyroid gland enabling the thyroid cancer to attract all iodine and thyrotrophin without competition from normal thyroid tissue Thyrotrophin in normal or increased amounts presumably enables the tumor tissue to take over a varying degree of function of the normal gland Regardless of the theoretical explanation the removal of normal thyroid tissue is important for the induction of I^{131} uptake in thyroid cancer Normal thyroid tissue collects iodine more readily than malignant tissue and its removal affords the neoplasm the sole opportunity of collecting the isotope Furthermore in the presence of myxedema thyroid cancer may develop an ability to produce thyroid hormone in varying amounts For hormone production iodine must be collected and stored and if the iodine is radioactive cell destruction will result

Dobyns and Maloof [15] as well as Rawson Rall and Peacock [38] have demonstrated that total thyroidectomy will induce or increase the functional capacity of thyroid carcinoma The increase in function thus achieved has been of sufficient degree in some instances to render the patient either euthyroid or hyperthyroid In almost all instances the degree of induced or increased function was sufficient to allow in vivo counting over the appropriate tissue

In addition to total thyroidectomy thyrotrophic hormone and prolonged administration of thiouracil combined with total thyroidectomy have been utilized in the induction of iodine uptake in thyroid cancer Thiouracil added to total thyroidectomy has established itself as an effective procedure for increasing iodine retention in thyroid cancer in those instances where thyroidectomy alone appears inadequate [39] Here again the presence of follicular components in the cancer has been associated with the successful induction of iodine uptake by thiouarcil Propyl thiouracil has also been utilized but has not been as effective as thiouracil

The mechanism of iodine avidity following thiouracil ingestion is not clear but two possibilities are advanced by Rall and his associates [33] First thiouracil causes severe iodine depletion so that iodine avidity in any functioning thyroid tissue will be very high as after prolonged maintenance on a low iodine diet Second large doses of thiouracil may augment the action of endogenous thyrotrophin as has been demonstrated by the experimental work of Albert and his co workers [40]

areas did take up I^{131} either in the primary tumor or in metastases the iodine appearing usually in the alveoli The highly malignant tumors, such as the giant cell carcinomas the Hurthle cell carcinomas and other more anaplastic tumors rarely concentrated I^{131}

Fitzgerald and Foote[3] found that 46 of their 100 specimens of thyroid cancer demonstrated radio-autographic evidence of uptake in carcinoma tissue Uptake in metastases usually paralleled that of the primary lesion when normal thyroid tissue remained While the concentration of the isotope was chiefly in colloid producing areas important exceptions to this rule may occur and thus prediction of uptake from morphology is uncertain in any single instance The distribution of I^{131} in areas where it is concentrated is uneven and almost never approaches that seen in the normal thyroid gland, which has greater avidity or trapping capacity for the isotope than the carcinomatous tissue

Radio-autography is more sensitive in the demonstration of iodine uptake than the external counter since it can demonstrate isotope concentration in a single thyroid follicle which could easily escape detection by the counter when enclosed in a large mass of non radioactive tissue

Fitzgerald and Foote s evaluation of I^{131} concentration by thyroid carcinoma has been confirmed by Dobyns and Maloof[15] in their study of 119 cases These authors also found that follicular adenocarcinomas collected more I^{131} than other thyroid cancers although the amount collected was much less than that of the normal thyroid gland Again they found a general correlation between histologic pattern and I^{131} uptake with some exceptions a few follicular adenocarcinomas took up no isotope and an occasional anaplastic or pure papillary tumor took up small amounts of I^{131}

Methods of Increasing the Uptake of Radioactive Iodine in Thyroid Cancer

Although 50 per cent of thyroid carcinomas will show some uptake of I^{131} by radio-autography only a very small number of these no more than 15 per cent will collect a concentration of I^{131} that will be tumoricidal This is true of carcinomatous metastases as well If the thyroid cancer cell could be induced to take over the iodine concentrating or hormone synthesizing capacities of the normal thyroid cell then destructive doses of internal radiation could be delivered into the cancer whether in the neck or in pulmonary or osseous metastases Seidlin[3] first demon

tracer dose of radioactive iodine is also useful if the metastases retain iodine

Cope[4] has demonstrated that a lymph node or group of lymph nodes, called by him the *Delphian nodes* (after the oracle of Delphi) and situated in the midline of the neck just above the upper border of the thyroid isthmus and anterior to the middle cricothyroid ligament is frequently involved and therefore palpable in thyroid cancer The node or nodes is superficial lying just posterior to the skin and first cervical fascia and is more often solitary than multiple While occasionally palpable clinically it is more readily visualized at operation and should be considered one of the important diagnostic signs of thyroid cancer However it is almost as frequently encountered in Hashimoto s thyroiditis and occasionally in association with diffuse hyperplasia of the thyroid

Tumor size is not helpful in establishing the diagnosis of thyroid cancer since very small nodules less than 5 mm in diameter may be the primary site of carcinoma The *age of the patient* is significant since thyroid nodules in childhood and early adult life are very likely to be papillary adenocarcinoma

A solitary nodule of the thyroid which by directional counting concentrates more radioactive iodine than the perinodular thyroid tissue may be regarded as a hyperfunctioning nodule and therefore probably not carcinoma A nodule with a decreased or absent uptake of radioactive iodine may be benign or malignant and should be evaluated clinically

The diagnosis of cancer of the thyroid in most instances will depend finally therefore upon pathological examination of the surgically excised nodule or nodules On this basis we have advised removal of asymptomatic nodules in most patients never permitting delay when the nodule is very firm or the patient is young Observation of the nodule has less hazard when it is soft or completely calcified In older patients with associated diseases in other organs that seriously limit life expectancy observation alone is justifiable provided the nodule is not interfering with respiratory function by tracheal pressure

Treatment of Benign and Malignant Neoplasms of the Thyroid

The treatments of benign and malignant neoplasms of the thyroid are best considered simultaneously because the clinical differentiation between the two types of neoplasm is often impossible without surgical

Diagnosis of Thyroid Cancer

The clinical diagnosis of advanced cancer of the thyroid is seldom difficult since all cardinal signs and symptoms are usually present These include (1) a history of recent growth (2) a hard irregular mass involving all or part of the thyroid which is firmly attached to surrounding tissues (3) *enlargement of regional lymph nodes* (4) *involvement of* the recurrent laryngeal nerve with voice changes and (5) pulmonary or osseous metastases This picture is rarely encountered however in most patients with thyroid carcinoma and the clinical diagnosis is actually very difficult There is a diversity of opinion about the accuracy of pre operative diagnosis of thyroid cancer ranging from Crile's[8] estimate of 90 per cent to Lange's and MacLean's[41] estimate of 14 per cent We feel that both figures represent oversimplification in view of the difficulty of pathological diagnosis in many cases coupled with the low growth potential of a considerable proportion of the tumors Our own experience emphasizes the difficulty of pre-operative diagnosis and the necessity of a perceptive attitude on the part of the surgeon during the operation Any degree of adherence of thyroid nodules to the trachea, recurrent laryngeal nerves or surrounding muscles should be considered as probably indicative of thyroid cancer Frozen section examination is helpful and should be generously employed particularly in establishing the papillary nature of the tumor Nodules that show any adhesiveness or those of a papillary nature should be treated as cancer

When cancer of the thyroid is limited to a single nodule and this is the usual situation the diagnosis may be suspected pre-operatively in many instances by a history of growth by the firm consistency of the tumor and by the presence of metastases in neighboring lymph nodes lungs or bones The history of growth however is not necessarily present since the papillary adenocarcinomas constituting over 50 per cent of thyroid cancers may be slow in growth The *firmness of the tumor* is of considerable aid in diagnosis but an appreciation of the consistency of the tumor depends upon proper examination techniques in which the nodule itself is cleanly grasped and palpated by the examining fingers without regard to overlying thyroid tissue of a normal consistency The *search for metastases* in the case of nodules suspected of malignancy should include careful examination of the neck for regional lymph node enlargement, examination of the vocal cords and roentgenography of the chest It is rare to have osseous metastases without concomitant pul monary invasion External screening or scanning of the body after a

tracer dose of radioactive iodine is also useful if the metastases retain iodine

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TREATMENT OF BENIGN AND MALIGNANT NEOPLASMS OF THE THYROID

The treatments of benign and malignant neoplasms of the thyroid are best considered simultaneously because the clinical differentiation between the two types of neoplasm is often impossible without surgical

investigation The primary treatment and the best treatment when applied in time, is by thyroidectomy The extent of the thyroidectomy and the necessity for simultaneous or subsequent radical neck dissection are at present a matter of some difference of opinion The factors that need consideration in deciding upon the proper operative procedure are (1) the pathological nature of the neoplasms and its potentialities for growth and metastasis, (2) the extent of intrathyroidal involvement by the tumor, (3) the degree of extrathyroidal invasion or metastases, (4) the route of metastases whether by blood vessels or lymphatics, and (5) the age and condition of the patient

The commonest malignant neoplasm of the thyroid is the papillary adenocarcinoma This constitutes from 50 to 70 per cent of thyroid malignancy in all recently reported series This type of carcinoma is undoubtedly slow-growing, both as the primary tumor and in its metastases It is necessarily late to metastasize, however and while the metastases are chiefly to the cervical lymph nodes, blood vessel invasion may occur with dissemination particularly to lungs and occasionally to bones Since this tumor also encapsulates itself poorly, it occasionally spreads diffusely throughout the thyroid gland invades the capsule and spreads to neighboring structures, especially the muscles and trachea Furthermore local recurrence after enucleation of the initial tumor is not uncommon The follicular adenocarcinoma and the angio invasive adenomas are often readily removable by simple excision without local recurrence but early metastases to bone are common followed by late metastases to regional lymph nodes and the lungs Malignant papillary cystadenomas of the thyroid are uncommon grow very slowly meta stasize chiefly to the lateral cervical glands and may remain of small size even with significant gland metastases

The more malignant tumors of the thyroid, namely the alveolar and solid carcinomas as well as the small cell carcinomas (carcinoma simplex) have a high growth potential and spread to muscles trachea, esophagus and lymph glands occurs at an early stage Surgical removal of this type of tumor may not be at all feasible because of the extent of involvement when the patient is first seen

The treatment of the papillary adenocarcinomas is controversial in regard to the extent of the operative procedure Black[4] and Crile[13] agree that total lobectomy is an obligatory procedure for the treatment of carcinoma limited to one lobe of the thyroid and entirely intracapsular since subtotal lobectomy is a demonstrably inadequate operation[4] Total lobectomy should be done whether the tumor is a papillary adeno

carcinoma a follicular carcinoma or an angio invasive adenoma Crile[43] feels that total lobectomy is indicated for all suspicious nodules of the thyroid Neither of these surgeons advises prophylactic neck dissection if there are no metastases beyond the thyroid Cattell[44] on the other hand considers neck dissection essential for such patients if the pathological diagnosis is that of malignant papillary cystadenoma papillary adenocarcinoma or alveolar carcinoma but is content with lobectomy alone in the presence of angio-invasive adenoma In a series of 3 patients subjected to neck dissection for thyroid carcinoma at the Lahey Clinic — carcinomas consisting for the most part of malignant papillary tumors alveolar carcinoma and carcinoma simplex — almost 90 per cent had malignant involvement of the removed lymph glands Cattell advises the removal by block dissection of the following structures the prethyroid muscles including the sternohyoid sternothyroid and omohyoid muscles together with the sternocleidomastoid muscle the internal jugular vein from beneath the angle of the jaw to the clavicle and the deep cervical chain of nodes

Lahey and Hare[45] consider radical neck dissection on the affected side essential under the following conditions (1) in all carcinomas that have spread through their own capsule into surrounding thyroid tissue in the same lobe and (2) in all cases without capsular invasion which show the histology of alveolar adenocarcinoma or of small cell giant cell or Hurthle cell carcinoma particularly if they show blood vessel or lymphatic invasion In papillary adenocarcinomas that have not invaded the capsule and are free of blood vessel or lymphatic invasion Lahey and Hare do not employ radical neck dissection

Black[4] found lymph node involvement in only 40 per cent of his cases of papillary adenocarcinoma and does not perform neck dissection unless the nodes are grossly involved Metastatic deposits to the nodes remain confined for prolonged periods and virtually never extend so far locally that the node cannot be removed Crile[43] is in substantial agreement with this point of view Our own experience with the surgical treatment of papillary adenocarcinoma corroborates the fact that total lobectomy and even subtotal lobectomy is followed by remissions of many years[5] Recurrence will be more likely with more malignant and infiltrating lesions when the primary operation is conservative

When both lobes of the thyroid are involved by carcinoma surgical therapy is difficult except in the instance of a slow growing tumor that has not spread beyond the capsule of the thyroid In these circumstances total thyroidectomy should be performed Ordinarily bilateral involve-

ment is associated with invasion of the thyroid capsule and the surrounding tissues and complete ablation is not feasible In such instances an attempt should be made to extirpate as much as possible of the involved thyroid in order to reduce or prevent the onset of pressure symptoms while non surgical therapy is employed When total thyroidectomy is performed, identification and dissection of the recurrent laryngeal nerves *are essential to prevent permanent damage to these structures* Total parathyroidectomy is occasionally unavoidable but is not so difficult a complication to control as permanent bilateral vocal cord paralysis

In the absence of distant metastases the treatment of thyroid cancer that has spread beyond the thyroid capsule depends upon the extent of fixation to adjacent structures in the neck When the thyroid is completely fixed lacking any degree of mobility, surgery is hazardous and gives little benefit and almost never a cure Biopsy of the thyroid however is always indicated even in the most advanced cases for diagnosis of the type of tumor and the possible application of internal or external radiation

As regards the surgical treatment of contiguous areas of lymphatic and vascular spread we find ourselves in agreement with Black[4] On the basis of experience at the Mayo Clinic he finds that the question of radical neck dissection arises primarily with papillary adenocarcinoma The angioinvasive adenomas and diffuse adenocarcinomas are usually inoperable by the time spread has occurred to adjacent structures Lymphatic spread occurs late with the malignant angio-invasive tumors and is rare until the thyroid capsule has become involved Involvement of the regional nodes is ordinarily associated with inoperable lesions In the case of the more malignant adenocarcinomas radical excision of adjacent tissues is rarely feasible unless the primary lesion is small and within one lobe

With papillary adenocarcinoma Black[4] is in favor of a limited type of neck dissection consisting of removal of the anatomic group or groups of lymph nodes draining the area of the metastatic growth Bilateral spread of papillary adenocarcinoma occurs only when the isthmus is involved At the initial operation careful search for lymph node involvement should be made in the upper and lower jugular group of nodes the anterosuperior mediastinal nodes and those immediately adjacent to the thyroid especially in the tracheo esophageal groove since these are involved in 70 per cent of all cases in which there is any lymph gland spread Recurrent nodes in undissected areas may be readily dealt with at secondary operations

Radioactive Iodine (I^{131}) in the Treatment of Thyroid Cancer

When thyroid cancer cannot be removed completely by thyroidectomy or radical neck dissection or both because of local or distant metastases radioactive iodine is a useful therapeutic agent in those tumors that concentrate or may be induced to concentrate adequate amounts of the isotope Enough cases have been studied and treated so that the indications for and limitations of radioactive iodine therapy are established

The largest series of thyroid carcinoma treated with I^{131} have been reported by Rawson Rall and Peacock[38] and by Dobyns and Maloof[15] Seidlin[37] has reported 12 patients whom he was able to follow for 6 years We have utilized radioactive iodine in the treatment of metastatic thyroid cancer since 1948 and in accordance with the experience of other investigators have found it of considerable value in a limited number of cases[46, 47]

Radioactive iodine therapy is limited on the one hand by the fact that most thyroid carcinomas and their metastases do not collect therapeutically effective quantities of the isotope and on the other hand by damaging effects of I^{131} on the other tissues The natural lack of avidity of thyroid cancer for radioactive iodine is by far the more significant limiting factor With radio autographic techniques about 50 per cent of thyroid carcinomas will exhibit some retention of I^{131} the amount retained however is rarely enough to effect destruction of thyroid cancer particularly in view of the irregular deposition of the material and its short range of destructive penetration External measurement of I^{131} uptake by a directional counter either Geiger Muller or scintillator or measurement of total body retention of I^{131} through studies of urinary excretion has supplied a more satisfactory index of potentially treatable lesions When uptake over a metastasis or primary lesion is in the euthyroid or hyperthyroid range then cancericidal doses can be delivered Similarly when total body retention of I^{131} is in the same range in a patient with thyroid cancer previously rendered myxedematous radio active iodine therapy will prove effective

In rare instances pulmonary and osseous metastases from thyroid cancer may have enough uptake so that destructive doses of I^{131} can be delivered For example our patient with papillary adenocarcinoma adequately removed from the neck by lobectomy had suffficent thyroid tissue remaining in the neck to maintain normal thyroid function A pulmonary metastasis retained enough radioactive iodine so that it was destroyed

along with the residual normal thyroid lobe myxedema ensued and there has been no carcinomatous recurrence after a 7-year interval [46] Seidlin [37] has reported a similar case with osseous metastases which not only exhibited primary uptake of I^{131} but also produced excessive thyroid hormone with clinical signs and symptoms of thyrotoxicosis

Thyroid cancer demonstrating primary uptake of radioactive iodine in either the parent lesion or its metastases is rare unless the lesion is chiefly follicular with colloid containing follicles as in benign metastasizing goiter or in follicular adenocarcinoma In the papillary tumors which constitute the bulk of thyroid carcinomas, and in the more malignant alveolar, solid, and small cell carcinomas primary uptake is exceptional The induction of uptake of therapeutically useful amounts of I^{131} is therefore an essential procedure in dealing with surgically ineradicable tumors of the thyroid and their metastases

The physiological considerations governing the induction of I^{131} uptake in thyroid carcinoma have been elaborated The most important step is the removal by surgery or destruction by radioactive iodine of all remaining thyroid tissue so that complete myxedema develops leaving the thyroid cancer cells as the sole potential repository of I^{131} and the only end organ for thyrotrophin activity Thiouracil in daily doses of 600 to 1500 mg may be added if myxedema alone proves inadequate for the development of function We have seen uptake appear 4 months after a patient had been rendered myxedemic with radioactive iodine others have noted it even earlier [15, 38] For the development of optimal uptake it is essential that the myxedematous state with or without added thiouracil should persist for several weeks to many months even to a year or longer Tracer studies can be repeated at regular intervals to determine the degree of uptake or retention of I^{131}, if the patient is receiving thiouracil it must be omitted at least 48 hours before the tracer is done Uptakes or body retention in the hyperthyroid zone should be reached for maximal benefit and can be attained in some patients The increase in avidity may be gradual or sudden External irradiation or non cancericidal doses of I^{131} may have an inhibitory effect on the development of uptake and should be avoided

The better method for the induction of myxedema is probably through the use of I^{131} rather than by thyroidectomy because I^{131} will more certainly destroy all normal thyroid tissue whereas total thyroidectomy often fails to accomplish this even though it can frequently produce clinical hypothyroidism Szilagyi and his associates [49] have demonstrated that after total thyroidectomy 55 per cent of cases will show some I^{131}

uptake in the neck and that 23 per cent of cases will remain euthyroid. We have been able to increase the degree of hypothyroidism following thyroidectomy by subsequent doses of I^{131}.

Complete athyreosis is not a tolerable state for many patients and is a serious problem when radioactive iodine uptake requires months to develop. Occasionally psychoses or profound disabilities necessitate the administration of desiccated thyroid for temporary periods. Some patients tolerate myxedema surprisingly well after an initial period of discomfort and can be so maintained for a long time.

The deleterious effects of radiation from I^{131} in high dosage is a second limiting factor in the treatment of thyroid cancer. This occurs particularly during the transport of the isotope through the blood in cases with little carcinomatous retention. In these circumstances there is a potential radiation hazard to sensitive tissues. Since the bone marrow is most frequently affected, lymphopenia, thrombocytopenia and anemia may develop. Occasionally temporary or permanent amenorrhea will develop following massive doses of I^{131}. The effects on the hemopoietic system is the most serious hazard of I^{131} therapy but can be minimized by keeping the therapeutic doses below the level that is harmful to the bone marrow. If the tumor concentrates I^{131} and does not release it rapidly as thyroid hormone, very large doses can be given without harm to extrathyroidal tissues. If, however, there is little concentration of I^{131} in the cancer or a high concentration with a rapid turnover or discharge from the tumor, then the dose must be reduced. Rawson and his associates[34] determine the daily blood levels of I^{131} for 4 days after a tracer dose and aim to deliver a therapeutic dose that will deliver less than 500 r.e.p. to the blood. Since the cancericidal dose for a given lesion cannot be determined, the largest dose that can be given with safety should be utilized.

X-ray Therapy

External irradiation of the thyroid region has been utilized for (1) inoperable cancer, (2) residual cancer after thyroidectomy and (3) prophylaxis after adequate thyroidectomy. In our experience x-ray therapy has not proved useful for the treatment of the more malignant tumors and has not prevented the recurrence of papillary adenocarcinoma after thyroidectomy. It has occasionally caused a striking regression in thyroid carcinoma of various types but we have seen no evidence that it is curative. Newer methods of applying external irradiation may make it more useful both prophylactically and therapeutically by enabling the delivery

along with the residual normal thyroid lobe, myxedema ensued and there has been no carcinomatous recurrence after a 7-year interval[46] Seidlin[37] has reported a similar case with osseous metastases which not only exhibited primary uptake of I^{131} but also produced excessive thyroid hormone with clinical signs and symptoms of thyrotoxicosis

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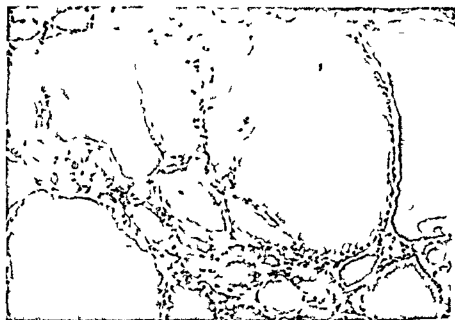
Fig 67



B *Fetal adenoma of thyroid* Microfollicles separated by a loose stroma which is for the most part optically empty The follicle lining is well defined and cuboidal Little colloid Hematoxylin and eosin ×90

of adequate irradiation to the cancer with less harm to contiguous tissues Irradiation dermatitis is a possible sequel to externally applied roentgen rays and may give rise to troublesome skin reactions in later years including skin carcinoma Tracheitis and esophagitis are frequently severe and distressing for prolonged periods after therapy

Fig 67



A *Colloid nodule* Follicles of uneven size but generally much larger than in normal thyroid tissue Colloid conspicuous by its volume it is smooth and moderately eosinophilic and displays retraction vacuoles at the periphery The lining epithelial cells are somewhat flattened Hematoxylin and eosin ×90

Fig 67



D *Papillary cystadenocarcinoma* The papillae rest on delicate vasculo-connective tissue stalks and are lined by rather orderly looking columnar cell perpendicularly polarized Nuclei tend to be basal No colloid deposition Hematoxylin and eosin ×90

Fig 67



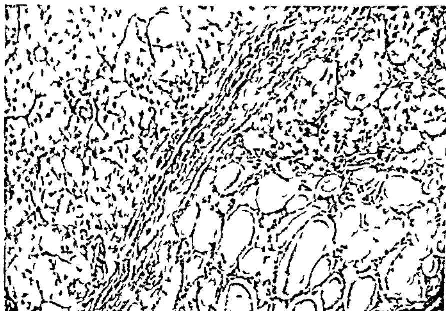
C *Embryonal adenoma* Pattern is trabecular or if lumina are formed tubular Compare with the follicular pattern of fetal adenoma Uniformity of epithelial cells Hematoxylin and eosin ×90

Fig 67



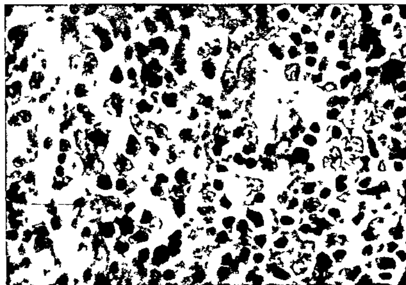
F *Adenocarcinoma* In contrast to Fig E the predominant structure is tubular rather than follicular The epithelial cells are tall columnar and well polarized There is nonetheless a good deal of cellular and structural anaplasia Density and distribution of chromatin vary many nuclei are vacuolated Hematoxylin and eosin ×90

Fig 67



E *Adenocarcinoma with follicular structure* There is virtually no colloid in the neoplastic acini The tumor extends alongside a septum and invades normal thyroid tissue in the right upper half of this microphotograph Hematoxylin and eosin x90

Fig 68



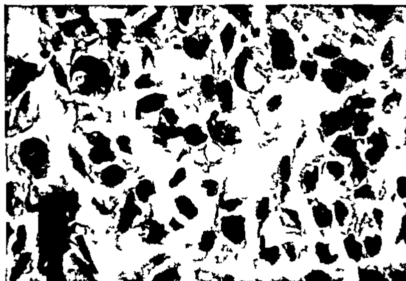
B *Small cell carcinoma high power view* Same slide as Fig A Pleomorphism of shape and size of the cells Many nuclei are pyknotic others contain prominent nucleoli surrounded by loosely arranged chromatin ×485

Fig 68



A *Small cell carcinoma* The thyroid gland is completely obliterated by vast numbers of small pleomorphic cells not displaying any pattern There is some resemblance to lymphosarcoma and indeed this type of neoplasm has formerly been so called For details see Fig B Compare with giant cell carcinoma Fig C Hematoxylin and eosin ×90

Fig 68



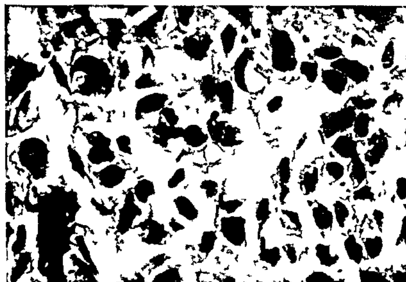
D *Giant cell carcinoma under higher power* Same field as Fig C Cytoplasm somewhat vacuolated x485

Fig 68



C *Giant cell carcinoma* Solid growth of a very pleomorphic epithelial neoplasm Many nuclei are not only very large but bizarre as well Marked hyperchromatism of nuclei To the left a residual thyroid acinus Hematoxylin and eosin ×90

Fig 68



D *Giant cell carcinoma under higher power* Same field as Fig C Cytoplasm somewhat vacuolated ×485

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CHAPTER XVI

MALFORMATIONS AND FUNCTIONAL DISORDERS OF THE GONADS

By WILLIAM ENGELBACH

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HISTORY

In the literature of the early eighteenth century first mention is made of a probable internal secretion of the gonads. The first lucid theory as to the internal secretions offered by Bordeu (1722–76) accentuated hypothetically the effect of the sex glands upon the individual organism as a whole. The striking

of the Skoptsi Russian religious fanatics who practiced castration upon children younger than ten years of age and the Lipovans of Roumania Skoptsi who had emigrated from Russia Two degrees of mutilation were inflicted the 'lesser and the greater seal (partial and complete castration) It is thought that in the female simple mutilation of the mammary glands rather than ovariectomy was effected The deductions of these authors were that the sex glands not only have to do with reproduction but are also an influence in the appearance and maintenance of the secondary sexual characters statural proportions distribution of adiposity and mentality This early research was a stimulus to the more recent investigations of the last decade relevant particularly to rejuvenation in the male (Steinach Voronoff Lydston Lespinasse and others)

The work most contributive to the projection of a hormone therapy of the sex glands has been the attempts of investigators to determine and define means of measuring the specificity of various gonadal extracts The experiments of Loeb relative to the sensitization of the uterine mucosa by secretion from the corpus luteum the discovery by Stockard and Papanicolaou of a specific type of cell present in the vaginal smear of small mammals during the oestrous cycle and the demonstration by Corner and Seckinger that the fallopian tube in domestic pigs undergoes definite contraction in the presence of specific extracts from the ovary have formed a basis for testing the potency of gonadal substances These controls have aided in recovering the developing of these extracts from the realm of theory and hypothesis They have led to more positive deductions in the elaboration of suspect hormones from these glandular tissues Their application in this regard is exemplified in the work of Adler Herrmann and Frankel Frank, Allen and Doisy and others

Embryology and Histopathology

Embryology

The interstitial cells of the male gonad become apparent when the embryo is 30 mm in length probably formed from Pfluger s cords At the stage of 1 0 to 150 mm the semen bearing cords can be identified (Lespinasse) The interstitial cells diminish in number the seminiferous tissue increasing from embryonic life to birth The interstitial cells cease growth until the age of puberty when they rapidly multiply Following the age of puberty they again degenerate to increase in later life They retain embryonic potencies in old age as shown by their ability to undergo differentiation and give rise to tumors as described in dogs by Goodpasture (Cowdry) According to Rasmussen they exhibit great cyclic changes in number in hibernating animals like the wood chuck They are reduced in number during the hibernating period greatly multiplying during active life and spermatogenesis Mulon believed that the

changes following castration in animals had been demonstrated by stock raisers and poultry fanciers, and the lack of development of the secondary sex characters in eunuchs, capons and spayed animals was depicted even at this early age The effects of the withdrawal of the testicular and ovarian secretions were an engrossing theme Various hypotheses have been advanced since then, which finally formed the basis for contemporary endocrinology and the idea of rejuvenation as expounded by Brown Sequard In 1849 Berthold through animal experimentation began to elucidate the gonadal secretion more vividly His experiments consisted of transplanting the testes of fowls to other portions of their bodies without disturbance of the sexual characteristics His conclusion was that the testes have a definite secretion, delivered directly into the blood and productive of specific effects

The more recent advancements pertaining to the gonads, particularly of the early twentieth century, were inaugurated by Robert Battey, of Georgia, in 1872 He conducted experiments in physiological surgery on women by resecting the ovaries for the relief of neuroses Brown Sequard in 1889, experimenting upon himself at the age of seventy two, reported that the extracts of the testes when injected into the human, produced a rejuvenation of the muscular power and mental activity There has been little confirmation of Brown Sequard s original work, and the effects he described have been considered in part at least due to suggestion Pohl later prepared a substance from the testicle, called spermin to which he ascribed a beneficial influence upon metab ol m and upon physical and mental activity He believed spermin to be the active principle of Brown Sequard s testicular extract Zoth and Pregel obtained a positive reaction upon the muscular and nervous energy *from testicular* extracts stating that they lessened fatigue Dixon disqualified the independent chemical composition or specific hormonic action of spermin and other testicular extracts He found them to contain a large amount of nucleoprotein and other proteins inorganic salts and some organic substances The only physiological reaction he attributed to their injection was a fall in blood pressure since then found common to other organ extracts as liver extract (MacDonald and Major) Glass (1899) Morris (1901), and Marshall and Jolly (1907) reported that transplantation of ovaries into ovariectomized women afforded considerable relief from symptoms of premature menopause and frigidity including secondary symptoms referable to other systems resulting from castration Lane Claypon and Starling (1906) demonstrated that the inhibitory influence upon impregnation and lactation of castration in the rabbit was not produced by ection of the nerves supplying the mammary glands or of the spinal cord They were among the first to demonstrate that atrophy of the uterus constantly followed castration Tandler and Grosz (1907–10) described the effects of castration in the human in both sexes offering the first presentation of the eunuchoid state Their information concerning the changes resulting from absence of the internal gonadal secretion during the juvenile age was in part obtained from their studies

lar elements The present consensus of opinion is that the source of the external testicular secretion is located in the seminiferous tubules That there is also an internal secretion having to do with sex differentiation as the secondary sexual characters the development and nutrition of the genital tract libido potency and the psyche of the individual is generally conceded The common theory is that this internal secretion is related to the interstitial cells of Leydig However no definite hormone has been isolated from the male gonad productive of the specific effects attributed to the internal secretion of these glands In clinical experience no preparation thus far supplied has over



Fig 1 — Sections of testicles (The Pituitary Body and Its Disorders Harvey Cushing 1910 p 2 8) A is from the testis of an eight year old boy having a syndrome of precocious sexuality Note the excessive interstitial tissue and abundant interstitial cells of Leydig with seminiferous tubules of preadolescent type B is from the testis of a potent individual who had never acquired complete secondary sexual characters Note the paucity of interstitial tissue with absence of cells of Leydig seminiferous tubules fully developed C is a section from the testis of an individual who was impotent and without secondary sexual character Note the absence of interstitial cells of Leydig and complete involution of the seminiferous tubules

come gonadal insufficiency in the male Nevertheless in many of the gonadal disorders the histology of the testis corresponds to the intensity of the sex characters as shown by Cushing He illustrates three types of human testis (Fig 1) in which the histological changes in the cells of Leydig and Sertoli s cells parallel the secondary sexual characters and spermatogenesis Unfortunately in females this relationship between the sexuality, secondary sex characters and histopathology of the ovary does not obtain

Swale Vincent summarily describes the anatomy of the ovary in mammalia as connective tissue stroma with blood vessels lymphatics and nerves enclosing the graafian follicles with the ova He states that at certain periods there

lipoid substance from these cells is the precursor of a true internal secretion from the testicle Iscovesco s experiments seemed to corroborate this

In the female gonad in the human (Pinto Seitz, Cesa Bianchi), but not in all specie there are present interstitial cells, which are of much earlier develop ment than the lutein cells They are well formed in the human embryo at the stage of 4 cm (v Winiwarter) Wallart asserts that they attain maximum de velopment before puberty, but persist throughout sexual life increasing during pregnancy According to Vincent, the interstitial cells of the ovary are much more conspicuous than those of the testis, and the histological differences be tween the two warrant hesitation in considering them in the same functional category Variant opinions exist regarding the function if any can be attributed to these cells Loisel has advanced the theory that the interstitial cells manu facture an internal secretion from their fat which secretion is productive of the secondary sexual characteristics in the male Many other authors consider them a factor in sex differentiation

Histopathology

The histology of the testis as described by Lespinasse is as follows The human testis is composed of lobules, formed by septa derived from the in vesting tunic of this organ These septa form pyramidal spaces having their bases toward the capsule and their apices toward the mediastinum The lobules consist principally of seminiferous tubules separated by connective tissue which contains the interstitial cells The epithelium of the convoluted seminiferous tubules consists of the columns of Sertoli and spermatogenic elements The cells of Sertoli are cylindrical structures, the basilar surfaces of which are in contact interwoven as a superficial network surrounding the epithelium of these tubules In the meshes of the reticulum are deposited numbers of plate like cells lying in contact with the basement membrane and also representing the sustentacular elements Between the sustentacular cells are found from four to six rows of cells possessing relatively large nuclei, rich in chromatin The cells of this epithelium vary according to the stage of de velopment finally maturing as true spermatozoa When isolated these tubules are seen to arise in the testis as closed canals which are closely coiled upon each other and describe a tortuous course until they finally reach the corpus Highmori The interstitial cells of Leydig are irregularly quadrangle scattered in groups through the connective tissue separating the tubules intimately related to the blood vessels and lymph channels The individual cell has an eccentri cally placed mass of condensed granular cytoplasm containing the nucleus while the external portion of the cell is extensively vacuolated The contents of the cell consist of fat pigment crystalloids and specific granules

To each of the cell contents has been ascribed some specific hormonic action Most of the investigators attribute the hormone to the lipoid and specific granu

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Swale Vincent summarily describes the anatomy of the ovary in mammalia as connective tissue stroma with blood vessels lymphatics and nerves enclosing the graafian follicles with the ova He states that at certain periods there

are corpora lutea and atretic follicles, and in certain species (50 per cent of 100 examined) the ' interstitial gland The cyclic changes in the ovary are ripening of the follicles, ovulation, and formation of the corpus luteum The phenomenon of the oestrous cycle occurring in the uterus consists of growth of the mucous membrane, with increased glandular activity, regression, and a subsequent quiescent interval The quiescent period is called the ' anoestrum ' The " pro oestrum is distinguished by increased vascularization of the reproductive organs culminating in the " oestrus " or " heat ', during which in the majority of animals the female will admit the male In the human and the primates generally, menstruation corresponds to pro oestrum in the lower animals If conception occurs oestrus is followed by gestation and lactation succeeded by another anoestrum If conception does not take place, oestrus is followed by metoestrum during which there is a return to normal on the part of the whole system

Sobotta s description of the histology of the corpus luteum is as follows In the mouse the epithelial cells are large and polygonal in shape measuring 20 micra or more in diameter They contain a substance known as lutein, a yellowish fatty substance which is for the most part disposed eccentrically, but may almost fill the cell This is present in larger amount in the central cells The older the corpus luteum, the more lutein it contains The body consists of columns of luteal cells, separated by intervening trabeculae, a fibrous tissue containing numerous blood vessels These trabeculae converge from the surrounding ovarian stroma to a central strand or plug of connective tissue (in which there are no luteal cells), occupying the axis of the nodule Among the cells are numerous cleft like lymphatic spaces a fully developed corpus luteum being a highly vascular structure The interstitial cells of the ovary are often difficult to identify They tend to occur in small clumps scattered throughout the stroma and possess large spherical nuclei often eccentrically placed and a fair amount of light staining cytoplasm vacuolated on account of the solution of its fatty constituents (Cowdry) They are reduced in number during hibernation in animals and increased at puberty and during pregnancy

To the present time no positive specific secretion has been isolated from these various ovarian cells and tissues The histological changes involved in the production of two types of secretion a serous and a lipoid as determined in the bat are described by Van der Stricht The serous secretion resembles liquor folliculi and is formed after the rupture of the follicle, by the young lutein cells It forms in tiny droplets within the cells is discharged into the intercellular spaces and passes into the lymphatics This serous secretion increases in amount during the segmentation of the ovum into two or three blastomeres decreases later and finally disappears completely when the egg reaches the uterus Van der Stricht maintained that it exercises a directive influence upon the sensitization of the uterine mucous membrane due to the oestrual changes The lipoid secretion is preceded by the accumulation of fat

in the lutein cells At first this fat blackens with osmic acid but later it becomes changed into droplets of lipoid which are excreted into the intercellular spaces and lymphatics Since the lipoid secretion begins shortly after the rupture of the graafian follicle and increases gradually until the end of pregnancy it is thought to be a factor in the arrest and fixation of the egg and the development of the placenta He considers it different from the hyaline material described by other authors

The existence of a second hormone possibly derived from the stroma or the interstitial cells of the ovary concerned with sex differentiation has been demonstrated by experimental results as in castration and ovarian transplantation although its successful elaboration has not yet been accomplished A valuable contribution toward evolving one of the specific ovarian substances was the work of Loeb confirmed by Ancel and Bouin Biedl and R T Frank pertaining to the relationship of the secretion of the corpus luteum to the cyclic histological changes in the uterine mucosa This work has been of great value as a measure of the specificity of a suspect follicular ovarian hormone Loeb demonstrated that the secretion of the corpus luteum sensitizes the uterine mucosa and makes it capable of reacting to mechanical stimuli This response was obtained only when sufficient secretion to sensitize the mucosa had been poured out The ovum became attached at about the time of greatest sensitization of the mucosa He found that the substance secreted by the corpus luteum which sensitizes the uterine mucosa was not specific for one individual The same substance caused growth in the sensitized uterus of a second individual of the same species with less effect than in the original organism This difference in effect was attributed to the presence of homoiotoxins in the second individual The experimental deciduomata in any species exhibited the structure of the maternal placenta in pregnancy In rabbits and guinea pigs the effects *were confined to the uterus while in the human deciduomata may be produced* in the fallopian tubes as in tubal pregnancy Extirpation of the corpora lutea prevented full size of the deciduomata and caused earlier and more extensive degeneration of those which developed Stockard and Papanicolaou (1917) demonstrated the presence of specific cells in the vaginal smears of small mammals during the oestrous cycle These researches proved an accurate means of determining the onset of what corresponds to menstruation in higher animals and therefore could be made the basis of a method of defining and measuring the potency of these ovarian preparations thought to have these effects upon the *vaginal mucosa Another development was the demonstration by* Seckinger based upon Corner s experiments of the cyclic variations in contractions of the fallopian tube in pigs by which he attempted to establish the physiological activity of ovrian extracts By suspending rings of fallopian tube muscle in oxygenated Locke s solution the normal contraction of the tube at the oestrous or the interoestrous stage of the cycle was registered on the kymographion The effect of the addition of various ovarian extracts to the Locke s

solution was thus registered and illustrated These control tests should be the means of identifying and standardizing at least one ovarian hormone, that exerting its effect upon the genital system It is a question whether they will serve to estimate that function of the ovaries influencing the secondary sex characters and constitutional sex peculiarities

Physiology

Positive evidence of the existence of an internal secretion of the gonads has been obtained from animal experimentation and operative procedure in the human Its physiological relation has been definitely established by the results of castration and gland transplantation The methods employed are auto- and homoplastic transplantation in the female, and to a less extent, homo and heteroplastic transplantation in the male Physiological experiments as summarized by Swale Vincent, are as follows Interference with the discharge of the seminal fluid (vasectomy) has no effect upon the secondary sexual characters while removal of the testes has a marked effect Similarly any operation in the female which abolishes the normal passage of the ova down the fallopian tubes into the uterus does not influence the secondary sexual characters while ovariectomy results in decided secondary sexual changes The effects of preadolescent complete ovariectomy have not been carefully observed or recorded Marshall has stated that double ovariectomy before adolescence prevents the onset of puberty and these individuals in adult life tend to the inverse sex stature His deductions are derived largely from the imperfect descriptions of Roberts who conducted observations in the East Indies It is doubted whether complete ovariectomy could have been performed successfully by these savages More likely mutilation of the external genitalia only was attempted Castration performed upon women after puberty is consistently succeeded by amenorrhea and a progressive atrophy of the uterus and external genitalia Some cases exhibit an atrophy, and others an increase in size of the mammae (probably due to deposition of adipose rather than glandular tissue) The sexual desire varies from frigidity to nymphomania The effect upon metabolism unless other ductless glandular involvement (as thyroid) follows the castration is negligible Headaches syncope, hot flushes and other nervous, cardiovascular, and gastrointestinal manifestations occur attributed to disturbance of the autonomic nervous system

Animal experimentation has demonstrated that in some cases the inverse sex characters are produced by castration in the female Atrophic degeneration of the uterus and fallopian tubes consistently resulted from these experiments Although some observers attribute these uterine changes wholly to interference with the blood supply or to damage of the nerve supply to that organ, evidence of an additional internal secretory influence is now fairly conclusive

Gonadal transplantation in the female has been accomplished for a con

siderable time with more or less positive result Autoplastic ovarian transplantation (grafting of the ovaries into other portions of the body in the same individual) in animals was first successfully accomplished by Knauer (1896-1900) He transferred the ovaries of rabbits and dogs from the normal position to the mesometrium or between the fascia and the muscle of the abdominal wall Atrophy of the uterus following castration was prevented by successful ovarian transplants Grigorieff (1897) reported pregnancy in four rabbits after the ovaries had been excised and replaced He also recorded two cases of successful transplantation of ovaries from one woman to another Ribbert (1898) reported that during the first months after transplantation the peripheral part of the ovary remained unaltered but the central part degenerated into connective tissue Later however the central portion again was found to contain follicles Morris (1906) reported the birth of a child in the case of a woman who had undergone ovariectomy and into whom the ovaries from another woman had been engrafted four years previous to delivery Halban and Limon found that transplantation of ovaries produced normal development (young guinea pigs) and prevented uterine atrophy (rabbits) Successful gland transplantation in animals has been performed by Magnus Guthrie Marshall and Jolly Steinach and Lipschutz A useful summary of recent work on ovarian transplantation in a human is given by Martin (1917) He concluded that from the standpoint of practical medicine the only form of ovarian transplantation of real service is autotransplantation Its value lies in reducing the symptoms of artificial menopause consequent to complete ovariotomy He maintains that the future of tissue transplantation in the case of the ovary as well as other organs and tissues rests upon a solution of the problem of the homograft It has been urged by some writers that retention of ovarian tissue after hysterectomy either in situ or by transplantation is of little or no physiological value and may be harmful (Craves 1917) The writer has noted in the majority of cases in which a portion of an ovary or a whole ovary was left at operation the development of classical signs of complete gonadal insufficiency The plausible explanation is that in many of these cases in which operation was undertaken for pelvic disease as salpingitis pelvic peritonitis etc and hysterectomy performed the blood and nerve supply to the ovaries was so impaired by the operation plus the pathological process that the retained ovarian tissue soon lost its function At least in many within six to twelve months the clinical picture closely simulated that of total ovariectomy in females of similar age

In the male recent transplantation experiments have been carried out by numerous observers (Steinach Sand Lipschutz Voronoff Lespinasse Lydston and others) According to Steinach s experiments the graft may last the life time in those animals which live only a few years The grafted animals ejaculated a secretion derived from the prostate and seminal vesicles containing no spermatozoa The seminal tubules in these grafts after transplantation were

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years Although the grafted testis had contained no spermatozoa histological examination a year after the graft was made revealed the presence of spermatozoa He employed the testes of anthropoid apes particularly chimpanzees in his human operations as he had found material from other species valueless He has reported 43 grafting operations in his recent publication (1923) He tates that the most critical period in the life of the graft is the first few days after implantation before its vascular connection is established He prefers the erous cavities stating that grafts made subcutaneously or intramuscularly are totally resorbed in a few months If the testis is small and young it is transplanted undivided but if it is large fragments are transplanted After carification of the tunica albuginea the graft is sutured to the testis or to the tunica avoiding direct contact between the parts of the graft The duration of the function of the graft is not stated but the effect persists for some time after absorption has occurred Experimenters in this field agree that all grafts ooner or later are ab o bed

Sand and Moore produced a condition of experimental cryptorchism by pushing the testes of rabbits guinea pigs and rats back into the abdom n through the inguinal canal severing the gubernaculum and closing the canal Atrophy of the tubules and increase in the interstitial cells followed this operation whether unilateral or bilateral The results of the e experiments were not those of castration as there was no effect upon the secondary sex characters or their subsequent development Sand Goodale and Pezard and Lespinasse in their experimentation on animals state that if the male gonad is succe sfully engrafted into the female the following changes occur (1) the mammary gland including the nipple shows no increase in growth (2) the uterus atrophies (3) the rudimentary organs as the corpora cavernosa of the clitoris are stimulated to growth (4) the body takes on the male status the nervous system is erotized in the male direction and the animal behaves like a male in every re pect Sand in these experiments reported successful grafts in rats although in guinea pigs the testes were always absorbed

Gonadal Extracts

The reproductive organs were the first glands suspected of having an internal secretion Although this early theory has been supported by later research the hormones from the sex glands apparently will be among the la t to be elaborated

Extracts from the Male Gonad

For more than two centuries a crystalline substance called spermin has been known to be present in the semen Leeuwenhoek in 1678 first described this substance and Vauquelin in 1791 rediscovered the compound During the

rarely found normal and finally disappeared, with the exception of the cells of Sertoli The grafted tissue usually showed a great increase in the interstitial substance in the form of compact masses between the degenerated tubules The transplanted testis finally became a puberty gland consisting solely of interstitial tissue Steinach maintains that, since the grafted animal grows to full maleness an internal secretion must be produced by the interstitial cells He found the sexual impulse in grafted rats above the normal and attributed this to excessive *development of the interstitial tissue*

Bouin and Ancel (1903) tied the vasa deferentia in different animals producing an atrophy of the seminiferous tubules without affecting the interstitial cells These authors were the first to call attention to the glandular appearance of these cells and suggested that the interstitial cells produce the secondary sex characters Ligation of the spermatic cord resulted in degeneration of the entire testis due to the loss of blood supply Steinach later used the method of vasectomy to produce rejuvenation He described experiments upon senile rats having an atrophy of the seminal vesicles and other sex organs, which were restored to a state of vigor and functional activity by vasectomy Gain in weight growth of hair deposition of fat change in general behavior, growth of the prostate and penis and increase in exual activity resulted Rejuvenation also occurred when only one vas was tied in which case the reproductive power was restored Steinach has reported successful operations of this type in the human but as yet the duration of these beneficial effects is uncertain Voronoff does not approve Steinach s method of unilateral vasectomy as he attributes the internal secretion to the whole testis and not especially to the nterstitial cells For this reason he recommends the tran plantation of the entire testicle As Vincent says "*it is too early to appraise the value of the e rival claims* and ' it must be remembered that unless blood vessel suture be employed grafting is at best a temporary expedient and the results can be good only when the material for the human comes from the testicle of the human or the anthropoid ape

The work of Voronoff falls into three groups (1) grafting experiments upon castrated males (2) grafting experiments in senile animals (3) grafting in human subjects Under the first group of experiments he reported that a castrated six months old goat retained its full sexual power and all secondary sexual characteristics for three years through the influence of grafts of testicles These were whole or in fragments engrafted into the scrotum Histological examination of the e grafts after a year revealed that some of the cells had become transformed into connective ti sue and the tubules no longer elaborated permatozoa although they must have furnished an internal secretion as shown by the condition of the animal His grafting experiments in senile animals are illustrated by the transformation of a decrepit ram twelve years old into a combative youthful animal by the engrafting of a gland from a six months old goat The animal became a sire and the effect of the graft persisted for four

there was reported a temporary gain in weight appetite sexual manifestations and general well being in most instances Three cases died due to the advanced stage of the disease In sixteen mental cases ranging from neurasthenia to manic depressive insanity, some improvement seemed to be noted One case of paranoia was reported to be free from delusions of persecution improving to such an extent that he was able and willing to work Almost all of the subjects reported increased sexual activity many claiming restoration of virility

Extracts from the Female Gonad

Prenant in 1898 suggested that the corpus luteum furnishes an internal secretion Federoff in 1899 reported the results of injecting ovarian extracts sub cutaneously and intravenously The only observation he made from such in jections however was that the pulse rate was lowered Knauer (1900) was the first to produce definite experimental data that the ovary was concerned with the phenomenon of oestrus and that the results of spaying an animal could be overcome in part by ovarian graft Theodore Landau first gave dried ovaries by mouth for relieving the symptoms of early menopause following double ovariectomy Mainzer (1903) repeated Landau s experiments describing a series of cases in which the symptoms consequent to total ovariectomy had been greatly benefited by the administration of ovarian tissues Frankel (1903) stated that he had obtained good results by the administration of corpus luteum It was not until 1912 when Adler published his account of the effects of in jecting animals with ovarian preparations that any attempt was made to con trol with accuracy the results of glandular therapy He stated that he was able by repeated injections of watery extracts of whole ovaries to produce menstrual periods and typical signs of oestrus in animals He checked his observations by histological investigations of the uterine mucosa and fully con firmed his earlier statements

Iscovesco (1912) published an account of the preparation of an active substance by extracting ovaries with alcohol He obtained a lipoid soluble in alcohol and ether from both the ovary and the corpus luteum Soon afterward Fellner published a paper in which he described a method for extracting ovaries with volatile solvents His preparation produced hyperplasia of the vagina and uterus He demonstrated that the extract was thermostable and soluble in alcohol ether and acetone Two years later Seitz Wintz and Fingerhut gave a detailed account of the preparation of lipoid material from the corpus luteum In the same year Okintschitz prepared extracts of the whole ovaries liquor folliculi and corpora lutea by grinding with saline and glycerol He named these products ovarin proprovar and luteovar respectively He at tempted to show that whereas the extracts from the ovary and liquor folliculi were active that from the corpus luteum was quite inactive Aschner (1914) produced rut like symptoms in castrated guinea pigs by injecting extracts of

following century Charcot and Robin, Friedrich, Harting, Bottcher, Forster, Salkowski Schreiner, Ladenburg and Abel, and Majert and Schmidt isolated this substance from various tissues and secretions of the body, identified it with, and differentiated it from known chemical compounds It was first thought to be one of the extracts of the male gonad having definite physiological effect upon not only the primary, but also the secondary sexual characters The investigations of Dixon and the recent publication of Dudley M C Rosenheim and O Rosenheim, which gives a full account of the chemical composition and physiological effects of this substance, have refuted the earlier claims for spermin It is now known that this substance is found in various tissues of the body, as well as in foreign material as yeast, and that it is physiologically inert

The oft quoted work of Brown Sequard (1889) notwithstanding its unauthenticated results, had the remarkable effect of reviving the experimental work of the preceding century directed toward the discovery of the gonadal hormone of both sexes Up to the present time comparatively minor results have been established with regard to any extract from the male gonad With the advent of the twentieth century however, important discoveries were introduced leading to an elaboration of specific substances from the female gonad Stanley (1921) reviewed the literature on male gonadal extracts from the time of Brown Sequard and reported his personal results from (a) the grafting of testicles from recently executed prisoners to senile recipients, (b) the grafting of ram s testicles into male prisoners and (c) the direct injection of testicular substances into the human subject More than 300 cases were treated with animal testicular material in this way These were unselected and consisted of neurasthenia, senility asthma paralysis agitans, epilepsy, dementia praecox, diabetes locomotor ataxia, impotence, tuberculosis, paranoia, gangrene of the toe atrophied testicles, rheumatism, and many other chronic illnesses not amenable to treatment From these experiments he concluded that animal testicular substance injected into the human body, does exert a decided effect Some of tho e receiving this treatment claimed that the eyesight was improved the appetite was increased there was a feeling of buoyance, a joy of living an increased energy loss of tired physical sensation, increased mental activity, and many other beneficial effects The author concedes that the results were difficult to e timate as it was necessary to rely largely upon the patient s statements He states however that when the psychology of a prisoner is considered one could be assured that if no beneficial effects were derived it would seem impossible to induce others to take the treatment However applicants came daily many insisting upon having more than the one injection to which the experiment was limited in each case Eight cases of asthma which were treated were helped four of which were relieved completely This was thought due to the possible increase of epinephrin induced by the injection of testicular substance In four cases of acne in young men of eighteen to twenty five years of age the eruption was markedly decreased Of eleven cases of tuberculosis

cells in both the surface epithelium and the glands They state that the growth and secretion processes in the genital tract induced by injections of active extracts into spayed rats and mice were equal to the maximum conditions normally attained in these animals under the secretion of their own ovaries

Their conclusions from this work are as follows (1) A determination of the amount of active substance extracted from different human genital tissues is made (2) This is measured in rat units by means of a decisive anatomic and physiologic reaction of the genital tract of the spayed rat to injected lipoid extracts (3) The follicular hormone is present in greater concentration in large ovarian follicles of women than in those of pigs (4) In pigs and cows the secretion of this hormone ceases or wanes rapidly after ovulation in women it is continued after ovulation by the corpus luteum for a considerable period (5) It seems possible that this may prove to be one of the principal determining factors in the difference between the oestrous cycle of lower mammals and the menstrual cycle of primates (6) Extracts have been made of placentas from women and cows which give the same growth reaction in test animals as does the ovarian follicular hormone (7) The human corpus of the first and third months of pregnancy contains some active substance but the placenta contains much larger quantities (8) The evidence presented indicates that the corpus can be excised as early as twenty days following the last menstruation without interfering with normal gestation consequently this endocrine function of the corpus in woman during this time does not seem a necessary one (9) Two possibilities present themselves to explain placental endocrine function either (a) the hormone extracted from the placenta is elaborated there or (b) it is retained there after being formed in the ovarian follicles or (in woman) in the corpus luteum They state that further experimental evidence is necessary to decide this point (10) Whichever proves to be the case the balance of endocrine function between ovaries and placenta offers a fertile field for more work In the discussion of this paper Novak believes that too much stress has been placed upon the role of the graafian follicle He does not think it all important in lower animals much less in women He suggests that the ovary is an organ of multiple interlocking function and that the graafian follicle the corpus luteum and the ovum itself are all important in this intricate but beautiful mechanism Carlson's criticism of this work is that a similar substance has been found in the placenta in the fetus and also in the corpus luteum of pregnancy in the human female He raises the question whether there are not various lipoid soluble substances present or whether a splitting of the substance does not occur in the methods of preparation and preservation In reply to Novak's objection Allen has stated that quantitative analyses so far have shown less active material in the human corpus than in the follicular fluid which he takes to indicate that the hormonal function of the human corpus in the absence of pregnancy is waning from a maximum attained by the follicle before ovulation In reply to Carlson's criticism Allen states that it is indeed

ovaries and placenta Itagaki demonstrated an increased tonus of the uterus, and Weil, an effect upon the respiratory exchange in animals, from ovarian extracts Abderhalden, Schiffman, and Gellhorn isolated ovarian bodies, called optones , and observed their effect upon paramoecia

The most painstaking chemical work in this field was done by Herrmann and Frankel in 1915 This was the basis of the preparations on the market known as 'corpus luteum *The physiological property of this substance, when in* jected subcutaneously, as stated by the elaborators, is promotion of the growth of the uterus ovaries tubes and vagina Premature sexual maturity can be produced in prepubertal animals and oestrus can be produced out of the rutting season by its administration Frank and his collaborators in 1915 and later published a eries of articles maintaining the importance of extraction of ovarian substance with lipoid solvents and prepared a series of substances similar to that of Herrmann and Frankel

Recently much of the interesting and valuable work done in early attempts to isolate an ovarian hormone, which until the last few years had been almost forgotten, has been revived on a more scientific basis The stimulus which has induced a considerable projection in this field has been the discovery of various methods of determining the specificity and measuring the potency of ovarian preparations, as mentioned under histopathology (Loeb Stockard and Papanicolaou Seckinger and Corner) The histological studies of Loeb have formed the basis for the identification of definite, specific substances in the graafian follicles Commencing in 1923, Allen and Doisy reported their re searches upon a specific substance in liquor folliculi Injection of this material produced puberty in prepubertal rats and oestrus *in castrated animals* A later paper, by Doisy, Ralls Allen and Johnston, described improvements in the preparation of this extract by which method all phosphorus containing sub stances together with inorganic salts were precipitated and a large amount of the inert fatty material was removed The amount of this extract necessary to produce these changes in an ovariectomized rat was considered a rat unit The weight of this varied according to the purity As small a quantity as 0 13 mg was found to produce this result

Allen, Pratt and Doisy in their last article review their previous work and abstract the recent literature on the subject of ovarian extracts They state that lipoid extracts of the contents of ovarian follicles quite completely substi tute for *certain phases of the internal secretion of the ovaries* This was demon strated by injecting extracts of material from pig ovaries into rats and mice from which the ovaries had been previously removed These experiments re sulted in an unusual growth of the female genital organs including (a) the pro duction within forty-eight hours of an entirely new epithelial wall in the vagina involving the addition of more than twelve layers of new cells (b) growth of the uterus with distention of this organ by the secretion of the glands which is retained by constriction of the cervix and (c) a marked increase in dividing

associated with the psychic phenomena of oestrus they emphasized the continuity and interaction of this triad by giving it the name of gestational gland They noted that rabbits deprived of thyroid suprarenals pancreas ovaries or various combinations of the ductless glands showed a ready response of the genital tract to the follicular hormone which they thought sufficient to prove that there was an absence of interaction of other endocrine glands in this reaction

Summarizing the development of gonadal extracts to date the most important deduction is that the dualistic structure and function of these glands have been ignored by investigators Simple external secretions have been credited with the attributes of internal secretions The external secretion of the testis derived from its spermatogenic cells was thought for centuries to contain specific elements influencing secondary and constitutional sexual peculiarities The recent work of Allen and Doisy and their coworkers which complements the earlier investigations of Adler Loeb Frankel Frank and others establishing the fact that there is a substance in the graafian follicles and lutein cells which sensitizes the mucosa of the genital tract is probably an exposition of the physiology of ovulation and oestrus The rupture of the graafian follicle and expulsion of the ova and liquor folliculi upon the mucous membrane of the tube and uterus is analogous to the excretion of the semen and its spermatozoa both fulfilling the requirements of an external secretion

The fact that experimentation has proved that the follicular hormone of Allen and Doisy or the corpus luteum of Frankel does produce oestrual changes does not indicate that these extracts are internal secretions of the ovary That there is an internal secretion of the ovary controlling the feminine ensemble has been proved by castration and ovarian transplantation This is probably apart from the external secretion derived from the ovarian follicle To date there is no preparation elaborated from the male gonad which given orally or hypodermically has any specific effect upon the primary or the secondary sex characters comparable to the internal secretion of the gland Homo and hetero transplantations of the male gonad on the contrary have exerted a transient influence upon genital growth and function as well as the constitutional male inclination

The conclusion from the available information on this subject is that the gonads have two different and distinctive functions the external secretion pertaining to procreation and the internal secretion to sex differentiation and the maintenance of these characters The external secretion in both sexes has been fairly well isolated and studied The existence of the internal secretions has been proved experimentally but these have not been positively identified or separated It is probable that the various ovarian preparations on the market contain some of the internal secretion in an impure form At least there undoubtedly are definite effects upon the symptomatology of female hypogonadism from their hypodermic administration

an interesting puzzle as to why the placenta (in women and cows) should contain this material However, since the follicular hormone may be extracted from the ovary of the hen, which species has neither corpus luteum nor placenta, the phylogenetic origin of this female sex hormone in the ultimate analysis must be referred to the follicle, or even to the ovum itself

Dodds and Dickens, working in conjunction with S Wright, have repeated Herrmann and Frankel s and Allen and Doisy s work, confirming their statements that a specific ovarian substance can be prepared consistently from ovaries by alcoholic extraction

Frank and Gustavson, with their co workers at the University of Denver and the University of Colorado, maintained that the female genital tract has but one purpose, that of reproduction, and that to accomplish this vital purpose, periodic sex cycles occur, of which the fertile sex cycle, and not the infertile, or abortive cycle is the normal type They confirmed to a large extent the work of Allen and Doisy, stating that potent follicular extracts will produce (1) premature puberty, (2) pregravid changes in the uterus vagina, and breasts of (a) immature animals and (b) castrates, and (3) the exaggeration of the pregravid changes to correspond to conditions of early pregnancy They refute the statement of Allen Doisy, Ralls and Johnston that all corpus luteum extracts are inactive, on the basis of their experiments on spayed albino rats, in which the vaginal spread proved the potency of such extracts They credit Iscovesco, Fellner, Hermann, Frankel and Fonda, Frank and Rosenbloom, and Frank with some of the early work in both the production and controls of these extracts Their work is convincing in so far as they have used the standard controls In their opinion the technique of Blair, which consists of suspending the uterus of a white rat in a chamber filled with oxygenated Locke s solution and estimating the variability of the spontaneous rhythmic contractions during and after oestrus is superior to the technique of Seckinger, who used the fallopian tube in much the same way They made histological studies of the endometrium and epithelial cells of the vagina and obtained positive results on immature and castrated animals They found that the obtaining of a specific substance from the corpora lutea of the hog and cow during (1) the early vascularized (bloody), (2) the later vascularized (bloody pink), (3) the flourishing (pinkish yellow) and (4) the involuting (yellow) stage was due to the technique of extracting or concentrating these substances The involuting (yellow) corpus luteum from these animals in the form of an alcoholic benzene extract was constantly potent, whereas in the other three substances specific reactions were absent unless an active extract was obtained by concentration, consisting mainly in the elimination of phosphatids, cholesterol, and cholesterol esters The amount of active hormone present in these latter three substances of the corpus luteum was proportional to the amount of cholesterol found As they found that follicular fluid corpus luteum and placenta all contain this active principle which induces hyperemia and hyperplasia of Muller s tract and the mammary gland sometimes

Tandler and others have questioned the diagnosis of complete aplasia in any cases thus far reported Those classified as such have occurred in the early and unsubstantiated literature Many of the historical cases of genital aplasia would now be considered as syndromes in which other glands influencing the development and function of the sex glands as the pituitary anterior lobe and the suprarenal cortex had been disturbed in early life A case observed by the writer might be thus classified owing to the atresia of the vagina The uterus and ovaries were not palpable through the rectum and to the age of twenty-one no menstruation had occurred Yet a careful interpretation would define this case according to a previous classification as a female bilobar hypophyseal insufficiency, with the anterior lobe primarily involved

Aplasia in the male

As to the male while the early literature describes some cases of anorchia (absence of the testes) it is a question whether they can be regarded as representative of entire absence of this endocrine tissue Probably they were a cryptorchism in which the testicles due to their failure to descend remained undeveloped making their demonstration difficult

Cryptorchism

Cryptorchism is a congenital malposition of the sex organs in the male in which one or both testicles are located intra abdominally or have descended only as far as the inguinal canal The undescended testicle is deficient in spermatogenic tissue or Sertoli s cells but has a hypertrophy of the interstitial substance These individuals differ from the majority of castrates attributed to the influence of the overabundant interstitial cells in the former In many cryptorchisms the secondary sexual characters are normal even though the primary characters are undeveloped The histopathological changes usual in these cases have been produced experimentally in the testicle by Sand Moore and others By reintroducing into the abdomen a normal testicle which had already descended into the scrotum and allowing it to remain for some time they proved that this change in location results in atrophy and loss of function of the spermatogenic tissue whereas the interstitial cells become hypertrophied These changes in the testicle are ascribed to the difference in temperature of the abdomen and scrotum

Hermaphroditism

The literature would tend to indicate that heterogeneous sexual development in distinction from aplasia of the genital tract is of greater frequency Whether

Anatomical Malformations

Malformations of the sexual organs comprise three general groups (*I*) Aplasia amorphia, anorchia, anovarism (incomplete or defective development of the genital tract) (II) Cryptorchism (aplastic undescended testicles) (*III*) Hermaphroditism (existence of characters of both sexes in the same individual) Hermaphroditism embraces two subgroups (from Pick's classification) (a) true hermaphroditism hermaphroditismus verus (double sex, or the presence of functionating organs of both sexes) (b) pseudo, or false hermaphroditism hermaphroditismus spurius (doubtful sex, or the presence of pseudo sexual characters either primary or secondary) Hermaphroditismus verus has three subtypes (1) contrasexualis (an ovary on one side and a testicle on the other) (2) heterosexualis (an ovary and a testicle on one side and either an ovary or a testicle, or neither, on the other), (3) homosexualis (an ovary and a testicle on both sides) Hermaphroditismus spurius has many conceivable subtypes as (1) internus (pseudo sexual development affecting the internal organs) (2) externus (affecting the external organs), (3) completus (a combination of internus and externus) (4) unilateralis (involving the genitalia on one side) (5) bilateralis (involving the genitalia on both sides) Subtypes, depending upon the involvement of the primary or the secondary sexual characters, are (6) primarius (in which the pseudo sexual characters affect the genital organs opposite to the prevailing sex type) and (7) secundarius (in which the secondary sex characters as hair distribution, voice, stature, etc, are opposite in type to the primary genital development)

Aplasia in the Female

Halban (1910) reviewed the literature on congenital aplasia of the ovaries Landau and Pick reported cases of neutral sex, who apparently had the secondary characteristics of one sex with absence of the primary gonadal function of that sex Pick reported an autopsy on an unmarried individual supposedly a female age fifty five, who had never menstruated The general type was masculine There were a clitoris 3 cm long and two enlarged ovaries The superficies was smooth no corpora lutea were found and the ovary had no parenchymatous tissue Howitz reported a similar case of a "neutral" individual in whom the hair distribution and pelvis were of the male type Large and small labia were present, and the clitoris was 6 cm long and 2 cm thick A urogenital fissure 7 cm long existed The history described a definite discharge of blood from the vagina at intervals of from one to several years from the thirtieth to the fortieth year At autopsy the ovaries were found to be of the size of an almond apparently without follicles The stroma was unusually hard and undifferentiated making indefinite the presence of the follicular apparatus

predominance of internal external or complete genital malformation There are al o subtypes depending upon whether the pseudosexual development is unilateral or bilateral and upon whether the primary or the secondary sexual characters are aberrant Heyn reported a very interesting complete pseudohermaphroditism (both internal and external genitalia involved) forty six years of age who had the secondary sex characters of the female This person was married at the age of twenty-one and sexual intercourse had been normal attended by orgasm and discharge At postmortem there were found a vaginal cul de sac and testicles but no uterus ovaries or prostate Many varieties of these p eudohermaphroditisms exist as may be seen by referring to Neugebauer s remarkable collection The writer has observed an individual of this type of female habitus who in early life had the inclination of the female attended a female seminary and for two years was engaged in a nurses training school in a reputable hospital After expulsion from this institution owing to a perversion of sexual habits this individual studied medicine as a male and assumed the practice of a specialty In order to acquire more masculine character various artifices were resorted to as tattooing the upper lip and pigmenting the hair and brows

Unilateral heterosexual development is considered as a peculiar predisposition in development due to a primary chromosomal deficiency frequently present in endocrine disorders According to this theory it cannot be attributed to a lack of growth or function of the sex organs which are thought to be the important factor in the production of the secondary sex characters

The important deduction from the study of these anatomical malformations of the generative organs concerns the relationship of the genital growth and function to the status of the individual These anomalies help to prove that the function of this endocrine tissue must be an influence in the general development and formation of the secondary sex characters of the bearer as well as the psyche mental inclination and accomplishment Two theories relative to the e relationships are expounded almost diametrically opposed (1) The sexual characteristics are inherited from the chromosomal gamete and continue to develop independently of the gonadal function This theory grants the existence of a hermaphroditic predisposition in both sexes and infers that the sexual glands exe cise only a protective stimulus in the development of the individual (2) The primary and secondary sexual characteristics are dependent upon the stimulus derived from the predominating generative organs

The former theory seems the more tenable when considering a hermaphroditism in which sexual glands of one sex coexist with the secondary sexual characteristics of the other or a condition of unilateral hermaphroditism Halban has cited that the heterosexual characters in hermaphroditism are developed prior to puberty and that uniovial twins are always of the same sex Recent experimentation in gland transplantation of the gonads of one sex to the other argues against the first hypothesis For instance Steinach transplanted ovaries into previously castrated young male guinea pigs and rats He successfully

a true hermaphroditism, with function of both sex tissues, has ever been demonstrated in the human is questioned Falta has stated that there are cases of so called ovotestis, which show in part graafian follicles and typical ovules and in part seminal tubules and Leydig's interstitial cells, without sperm Salen reported a case in an individual forty three years old, who had menstruated since the seventeenth year The clitoris was 5 cm long, the vagina was 6 cm in length the labia majora were normal, and the habitus was that of the female Simon refers to an individual twenty years old considered a male, at least according to sexual inclination Yet in this case menstruation had existed for



Fig 2 — Pseudohermaphroditism aged six Note the absence of trichosis differentiating this case from pseudohermaphroditism occurring with suprarenal cortex lesion (*Courtesy of Dr A G Bosler Chicago Illinois*)

three years and the secondary sexual characters were predominantly of the female There were a clitoris of 6 5 cm, an unperforated glans and well developed labia majora Autopsy revealed the presence of fallopian tubes, parovaria, and ligamenta lata Vasa deferentia and epididymis were without connection with the testicular part of the ovotestis The ovotestis was found to contain glandular tissue of both sexes but there was no evidence of activity of these tissues

The pseudohermaphroditic anomalies (Fig 2) are grouped according to the

gland primarily affected (1) hypophysis (pituitary) (2) epiphysis (pineal) (3) suprarenal cortex (4) thyroid

It is to be hoped that the above grouping which correlates the functional and anatomical changes in the sex organs and the resulting clinical syndromes with the age of their occurrence will simplify the interpretation of these varied complexes The functional derangement of gonadal tissue is productive of a definite constitutional reaction depending upon the age of onset and the extent of the disorder Aside from the changes affecting the generative organs and the secondary sexual characters the osseous development and the presence or absence of classical adiposities are the most constant general manifestations noted in these disorders The writer first made studies of positive cases such as early and late castrates By comparing the castrates with the eunuchoids a similarity of syndromes was noted varying with the degree of the disorder As an aid to the clinician in interpreting the clinical pictures of eunuchoidism from its varied symptomatology these gross measurable signs presented as disproportions in physique and contour have been emphasized Secondary symptoms particularly referable to the gastrointestinal cardiovascular and nervous systems are discussed under the various types to which they are common

Hypogonadism

Symptomatology —In a general consideration of the symptomatology of hypogonadism the sexes are discussed conjointly with emphasis upon minor differences It is found expedient to group the symptomatology in endocrine disorders as follows (1) general hormonic signs (2) regional hormonic signs (3) laboratory signs The laboratory signs are general hormonic signs which require special technique as basal metabolic or blood chemistry estimations

It can be stated that as a rule the general hormonic signs are more important indicators of aberrant glandular function than are the regional Even in those ductless glandular affections in which the localized changes are very obvious as thyroid enlargement or male gonadal disorder the general symptoms offer the more intimate evidence as to the glandular function It has not been possible to estimate the amount of specific substance or hormone in the blood even of those glands whose hormones have been isolated and synthesized as thyroxin Neither have histopathological studies been of much aid in determining the function of these glands In incretory disorders in many instances a proper interpretation of the effects of the glandular hormone upon other tissues of the body is of more value than a knowledge of the histological changes in the gland itself With these constitutional or general hormonic effects clearly understood it is possible to diagnose endocrine disorder even if the glandular hormone has not been positively elaborated These signs are of particular value in female gonadal disorder in which the size and conformation of the glands are not readily estimated In the male however the size form and consistency of the

demonstrated that the primary follicles of the ovary formed normal ova and corpora lutea developed in the transplanted gonads In addition, the penis in the male guinea pig ceased growth and even retrograded If, in addition, the uterus and a part of the fallopian tube were transplanted, these developed into mature organs In these male animals there occurred an unusual mammary development, not unlike that of the female, in some instances even exceeding in size the normal mammae of the female The osseous system hair growth and adipose deposition tended to assume the opposite sex type in these cases of transplant Biedl attempted to explain these heterogeneous sexual characters by the second theory as due to the internal secretion predominantly present This would also indicate the preponderance of primary sex characters in these individuals

Some of the signs ordinarily interpreted as gonadal such as hair growth localized adiposity etc may in some of these cases be due to primary disorder of other glandular tissues For example it is known that the hypophysis and the suprarenal cortex are often found to have disturbed function and structure in these peculiar hermaphrodites Particularly striking are the syndromes associated with disorder of the suprarenal cortex Females, who have been normal suddenly develop an amenorrhea associated with an unusual pigmentation hair growth and in some cases adiposity These hirsutisms and virilisms associated with deficient function of the gonads have led clinicians to suspect erroneously a primary anatomical malformation of the sex organs

FUNCTIONAL GONADAL DISORDERS

Classification — Functional gonadal disorders comprise two groups (1) hypogonadism (2) hypergonadism Hypogonadism has two subgroups, depending upon the degree of deficiency (a) complete (castrates), (b) partial (eunuchoid) The partial castrate who has had only a partial or a whole ovary or testis removed is grouped with the eunuchoid The castrates and eunuchoids are subdivided into (a) nonadipose or early type in which there is an abolition or a diminution of gonadal function before the adult age (twenty five) (b) adipose or late type in which this interruption of function with consequent changes occurs in the postadult age The nonadipose castrates and eunuchoids are subdivided into (a) preadolescent (b) postadolescent (maturity to twenty five years of age) The adipose castrates and eunuchoids have the following sub types (a) early adult (localized trochanteric adiposity) (twenty five to thirty three years of age) (b) late adult (generalized adiposity) (after thirty four years of age)

Hypergonadism has two subgroups (a) primary, (b) secondary In primary hypergonadism the disorder of the generative organs accounts for the genital as well as constitutional symptomatology Secondary hypergonadism is due to other ductless glandular disorder and is classified according to the

gland primarily affected (1) hypophysis (pituitary), (2) epiphysis (pineal) (3) suprarenal cortex (4) thyroid

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sex organs, and analysis of the spermatogenic function aid in determining the state of both the external and the internal secretion Before adolescence, even in the male, the genital function is conjectural unless one can depend upon factors other than the physical evidence in the testes In postadolescent life while examination of the semen will determine the spermatogenic activity, the general hormonic signs (secondary sex characters, stature, hair growth and othe dermal changes libido, potency, etc) help to estimate the internal testicular secretion The laboratory signs, as the basal metabolic rate, blood chemistry and the effects of the injection of glandular extracts (as determined by the blood pressure, pulse rate vasomotor disturbances, subjective symptoms oestrus, etc) thus far have proved of relatively minor clinical value

General Hormonic Signs — The four important general hormonic signs referable to hypogonadism are as follows, (1) variation in osseous growth ( ) specific deposition of adiposity, (3) dermal changes, (4) subjective symptoms general and systemic These signs vary depending upon the age at which the disorder is initiated and the age at which observed It is therefore necessary to classify them as characteristic of either preadult or postadult hypogonadism The symptomatology associated with castration and eunuchoidism is similar, the severity depending upon the degree of insufficiency of the glands However, the age of onset and the time of observation of the disorder must be considered for a proper conception of the various clinical syndromes

Changes in the *osseous system* constitute the *first gross hormonic sign* It is accepted by most expositors that there is an internal secretion of the gonads in each sex productive in the preadult age of fusion of the epiphyses with the diaphyses of the long bones Consequently, in hypogonadism, when this internal secretion is deficient the epiphyses fuse a number of years later than normally while in hypergenitalism (excessive secretion of these glands) epiphyseal union occurs too early The statural proportions and x ray observations of the bones at various ages in these cases are convincing evidence Recent studies of the osseous system comparing various endocrines with normal individuals (Engelbach and McMahon) have established this osseous sign as an accurate diagnostic guide in the preadult age In the hypogonadism, in which other hormones of osseous growth are normally present (the thyroid and the pituitary anterior lobe) the classical disproportion indicative of preadult gonadal insufficiency occurs due to longitudinal increase of the long bones, without marked changes in the short and flat bones The result is a tall, usually emaciated individual having the lower measurement (symphysis to soles of feet) much greater than the upper (vertex to symphysis) It is to be noted that the measurement most affected (lower) is made up almost entirely of long bones, while the upper consists of short and flat bones The span for the same reason is longer than the height The opposite developmental proportions are displayed in the hypergenital states in which the excessive function has occurred before the age of twenty five during the period of skeletal growth

The *second gross hormonic sign* affording a clinical interpretation of gonadal activity in the human and a differentiation of types is *the characteristic adiposity* which occurs in deficiencies of the sex organs A partial or a complete insufficiency of the gonads rarely if ever has any general or localized adiposity until the age of eighteen to twenty At that age more especially in the female there may appear a localized panniculus adiposus about the trochanteric regions as shown in Fig 8 Many eunuchoid males pass the early adult age (beyond thirty) without evidence of an adiposity which could be related to a deficiency of the sex organs In later adult life there consistently is present a generalized adiposity a rather diffuse infiltration throughout the body with pronounced localization at the mons trochanteric regions and mammae This generalized adiposity is also an earlier sign in the female (at about the age of thirty) In the male it rarely is present before the age of thirty four

These two predominant general hormonic signs osseous development and adiposity respectively of the preadult and the postadult age have been designated by the writer as differentiating the two main groups of hypogonadism (nonadipose and adipose) In the preadult age during epiphyseal activity the osseous changes with their consequent disproportion are a constant and dependable sign of a disturbed function of the sex organs During postadult life (after twenty five) when the epiphyses have fused and become inactive no skeletal change results Adiposity if present in these cases before the age of twenty five is localized in the trochanteric region while a classical generalized obesity is one of the constant signs of late postadult hypogonadism

The *third general hormonic sign* relates to *dermal changes and hair growth* The scant hair growth of eunuchoid individuals has been described for many years whereas a tendency to hypertrichosis exists in hyperfunctions of the sex organs This statement must be altered somewhat The hair on the scalp in hypogonadism is usually luxuriant long and coarse whereas the facial and bodily hair is scantier than normal The trichosis of hypergenitalism usually depends upon other glandular involvement The associated suprarenal cortex disorders have the most pronounced overgrowth of hair the anterior lobe pituitary involvements are next in this regard and the suspect pineal cases which have a marked hypergenitalism have only the ordinary bodily hair growth

In hypogonadism the skin tends to a soft velvety character overlying a cushion of pliable panniculus and lymphatic tissue It is delicate and sensitive to external and internal influences so that there is a predisposition to a so called *exudative dermatosis and to allergic reaction* In adult life the skin early begins to assume senescent changes with a brownish parchment like appearance and premature wrinkling With this exception there is no definite pigmentation consistently associated with hypogonadism In the uncomplicated case the chloasma of pituitarism the alabaster color of myxedema or the dirty brownish impregnation of Addison s disease is not observed

The *fourth general hormonic sign* is a marked *exhaustion and fatigue* This

fatigability is mental as well as physical, resulting in some instances in complete incapacity This sign is most frequent in the preadult age and at the menopause The writer has observed bedfast cases, unable to undergo even the slightest mental exertion The immediate relief of this state of inertia by ovarian substitutional treatment is clinical confirmation of its etiology, particularly when repeated in a series of cases in which other forms of general treatment have failed to produce measurable effects

The *subjective signs* and symptoms of hypogonadism refer mainly to the nervous cardiovascular, and gastrointestinal systems The history frequently suggests an organic lesion of one of these systems yet careful physical and special examinations are rarely corroborative Among the *nervous symptoms* are a pronounced general nervousness and various psychic states from emotionalism and excitation to depression and melancholy Headaches ocular and aural symptoms and general sensory disturbances referable to touch pain and temperature are characteristic Gross psychasthenic syndromes frequently adjudged to be hysteria are presented Among the *cardiovascular signs*, vasomotor disturbances as intermittent sensations of heat and cold, with general and localized flushing and pallor, are common Next in frequency are those referred by the patient directly to the heart, as tachycardia palpitation, precordial pain and distress an associated feeling of tightness in the chest, subjective dyspnea, orthopnea etc The *gastrointestinal symptoms* vary from mild gastric distress to prolonged pernicious regurgitation and vomiting Anorexia, pyrosis, gastric distention rumination and nausea are frequent Abdominal distention, associated with spasticity of the colon and mucous colitis is not as characteristic of these cases as of pituitarism Many of them, however have such persistent, intractable regurgitation and vomiting that the condition usually is diagnosed as local disease of the gastrointestinal tract or its adnexa The writer has observed cases of continuous vomiting of a duration of several months to fourteen years Nearly all have occurred in the female and are usually the preadult type of hypogonadism associated with cessation of the menses (see Fig 6–C) In some of these cases in which the insufficiency was not too extreme, this vomiting after exploratory operation without determinable cause, responded to substitution ovarian treatment Secondary symptoms referable to systems other than the nervous cardiovascular and gastrointestinal do not protrude into the picture There are few respiratory signs consistently present, except as related to pulmonary infection, to which this type of individual is susceptible

Regional hormonic signs — The regional hormonic signs consist of the anatomical and functional of which the latter are of first importance in diagnosis After adolescence in female complete hypogonadism (castration or extreme eunuchoidism) the menses are absent The female eunuchoid consistently has more or less pronounced menstrual disturbance Maturity is usually delayed until the age of fifteen to sixteen instead of occurring at the normal age of thirteen to fourteen (in the temperate zone) In many cases a normal

menstruation exists for two or three years with a flow of four to five days duration at regular intervals A composite picture of a large number of eunuchoid girls shows that usually at eighteen or nineteen there is a gradual decrease in the amount and duration of the flow without change in the interval This progressive lessening of the period from five to four to three days then to two days or one day is accompanied by an exaggeration of the associated dysmenorrhea After a two or three year course the duration of the menstrual flow may diminish to less than one day Concomitant with this abnormal function are secondary general and systemic symptoms as exhaustion cardiovascular manifestations and particularly at the preadult age gastrointestinal signs The severity of this latter symptomatology tends to parallel the degree of menstrual suppression In female eunuchoids having a complete amenorrhea before the age of twenty there commonly is a decided general nervous gastrointestinal and cardiovascular reaction while in some of the cases only one of these systems apparently is involved An occasional instance is noted of an intermittent menorrhagia interspersing various types of imperfect periods instead of the progressive loss of function as described above Dysmenorrhea is a frequent accompaniment of these menstrual abnormalities in primary gonadal deficiency

Differentiation of other conditions influencing the menses at this age must be considered Various local anomalies and diseases of the genital tract are known to produce imperfect periods and usually may be excluded by physical examination There are few ductless gland affections of any severity which do not modify the menstrual flow and sexual sphere Most of these are diagnosed first by the difference in age incidence of the menstrual disturbance and secondly by a history referable to other ductless glands In hypothyroidism for instance adolescence is initiated two to three years before normal puberty that is at ten to twelve years of age instead of at thirteen to fourteen In anterior lobe hypopituitarism as in hypogonadism maturity is delayed a year or two These two conditions tending to produce an amenorrhea in the preadult age are easily distinguished by the osseous make up Anterior lobe hypopituitarism has a retarded osseous growth resulting in shortness of stature opposite to hypogonadism Hyperthyroidism also has a late onset of the menses with amenorrheic and dysmenorrheic tendencies but has signs identifying this state as fast pulse tremor increased basal metabolic rate struma etc Debilitating and emaciating diseases as chronic infections also affecting menstrual function are differentiated by their symptomatology and the absence of definite genital or other endocrine signs

Diminished function of the ovaries producing menstrual imperfections after the adult age is not so common until later adult life After thirty four in primary hypogonadism there frequently is a tendency to amenorrhea or a complete amenorrhea In these cases a potential decreased ovarian function exists as evidenced in a previous irregularity or variation of the menstrual flow combined with the general hormonic signs of hypogonadism These late adult

types rarely have marked gastrointestinal symptoms, although they complain of nervous and cardiovascular disturbances The normal cessation of the menses, occurring in the majority of women living in the temperate zone at from forty two to forty five years of age, is rarely accompanied by marked symptomatology except in individuals who have some endocrine tendencies The hypogonad type for instance, has the most pronounced symptomatology, limited almost wholly to instability of the cardiovascular system consisting of hot flushes, tachycardia palpitation, etc The hypothyroid individual has a delayed onset of the menopause until the age of forty eight to fifty Many of these women become impregnated and bear children after the age of forty Their symptoms refer more to partial thyroid insufficiency than to gonadal disorder The pure pituitary insufficiencies are inclined to have their menopause before the age of forty Sterility, as well as frigidity is a concomitant clinical sign in these cases Their distressing complaints refer mostly to the nervous and gastrointestinal systems

The anatomical regional hormonic signs also depend upon the age incidence of the disorder If the deficiency has occurred before adolescence in either sex the external genitalia are undeveloped and infantile The demonstrable internal organs as the prostate or the uterus, correspond in development The size of the ovaries and tubes is difficult to define, particularly if the adiposity of late gonadal insufficiency is present However the uterus serves as an index to the internal genital growth and function The labia minora and labia majora are small and imperfectly formed, the clitoris difficult to differentiate The size of the genitalia, however, may be very deceptive with regard to their function In many males having comparatively small testicles there is a decided sex instinct, with virile, motile spermatozoa demonstrated in the spermatic fluid On the contrary, in some individuals of both sexes having well developed genitalia an absence of primary sexual function exists with normal secondary sex characters This is probably due to a hypertrophy of the interstitial substance of the testicle with a normal production of the internal secretion For this reason the libido potency, and procreative function cannot always be determined from the objective signs In the male examination of the seminal fluid and in the female the menstrual history offer more positive evidence than do the anatomical signs The pubic hair growth and mons adiposity depend upon the age and the time of onset of the gonadal disorder

The regional hormonic signs of gonadal insufficiency initiated in adult life must necessarily differ from the preadult signs described As at this age the genital system has been developed and functionating for a number of years, one would not expect to find an aplasia of these organs While it is true that some regression occurs owing to lack of function particularly of the external genitalia and prostate in the male it does not result in the infantilism of this system present in the early disorder This regression has been the basis for the castrate treatment of enlarged prostate Regression of the uterus also occurs, which how

ever is not in itself a positive clinical sign of hypogonadism and it is not possible to determine the ovarian function through this medium The decreased function of these organs is the more significant phase In the male there is a decided reduction in potency and libido an examination of the spermatic fluid if procurable shows an absence of motile spermatozoa Libido may not be entirely absent due to the presence of the interstitial cells in the eunuchoid In those males in whom there is an absence of the external secretion while the testicles are still present either in the scrotum or the abdomen libido often persists The writer has under observation an individual who has had one testicle removed and the vas deferens of the other resected Spermatogenesis has been absent for many years An unsuccessful attempt was made to perform an implantation of the vas into the remaining testis Although this testicle is disconnected from the vas prostate and seminal vesicle this individual has maintained a very normal potency and libido consummating copulation as often as three times a week Another case is a eunuchoid male who has a marked aplasia of the entire genital system yet who insists that he has a decided sexual instinct and regularly has erections and ejaculations from an infantile penis sufficient to attempt intercourse It is known that many of the cases of cryptorchism who have undeveloped testicles and have never had live spermatozoa in the seminal fluid differ from the early castrates in that they have the secondary sex characters and a libido which is probably somewhat below the normal Female hypogonadism also presents some unusual and vague sexual reactions For instance it is difficult to explain why some women who have been frigid develop after complete ovariectomy a decided sexuality with a libido above the normal A certain percentage who have been more or less frigid prior to the menopause change to a vicarious sexuality at that age

Among the extra genital regional hormonic signs the following description applies only to the preadult types of hypogonadism The head and facies incline to the long narrow configuration with anterior angulation The forehead and face usually present a triangular contour in contrast to the rounded facies of myxedema and the hexagonal type of pituitarism The features are delicate and sharply angled with the familiar receding chin rather long sharp nose and narrow mandibular measurement The characteristic orthodontial markings are large upper central incisors with decreased size or absence of the lateral incisors The other teeth are comparatively large and fairly regular without definite mal occlusion In the majority of early cases a tendency to dedentition exists In some it has been necessary to extract all of the teeth before the age of twenty and even in milder cases the teeth must be guarded against serious deterioration The larynx is undeveloped in early hypogonadism with a consequent high pitched voice The mammary and mons changes have been discussed under the obesity signs The conformation of the pelvis and genu is another characteristic sign In pronounced early hypogonadism the pelvis is wide in the male simulating the feminine type The male shows the genu valgum of the

female In the female there is no inversion of type in pelvis or genu, merely an exaggeration of the feminine character

Laboratory Signs — The laboratory signs (basal metabolic rate, blood chemistry estimations, reactions to specific substances, etc) have not developed into diagnostic significance In the uncomplicated hypogonadism there is a practically normal basal metabolic rate This test sometimes serves to differentiate gonadal obesity occurring in late adult life from myxedema In hypergonadism the basal metabolism may be disturbed, as some of these conditions are secondary to other glandular affections, in which case the primary glandular disorder might produce an abnormal rate To date there is no essential diagnostic value attached to the blood chemistry or the reactions to injection of glandular preparations, as thyroxin, pituitrin, adrenalin, or the various gonadal extracts

Nonadipose Hypogonadism

Preadolescent Variety — Nonadipose hypogonadism, embracing the pre adult castrates and eunuchoids, is subdivided into the preadolescent and post adolescent (maturity to the age of twenty five) varieties, according to the age at which the disorder is presented The two constant general characteristics of this group are the overgrowth of the long bones and the absence of obesity the long bone increase producing the disproportion previously described consisting of an upper measurement (vertex to symphysis) longer than the lower (symphysis to soles of feet) and a span exceeding the height This osseous sign is attributed to insufficiency of the gonadal function, with its sequence of delayed epiphyseal fusion, during the period of osseous growth (previous to the age of twenty five)

The writer maintains that in the preadolescent complete or partial insufficiency there is no associated adiposity The absence of adiposity, even of the localized trochanteric deposition (frequently occurring in the later postadolescent age eighteen to twenty years), seems to be a distinctive feature of this early group

There is very scant literature on the early castrates Roberts reports on the results of castration of infants in India cannot be confirmed Tandler and Grosz studies of the Russian Skoptsi (the Lipovans of Roumania) give us the most exact description of the symptomatology in the preadolescent castrate These authors first directed attention to the difference in general constitutional signs due to the age at which the castration was performed They refer to two types, the tall and the fat In complete hypogonadism due to castration in the preadolescent age they described a general defective development of the reproductive organs In the male the penis was very small and the corpora cavernosa penis were undeveloped, although the corpora cavernosa urethrae were unaffected The prostate was deficient in glandular tissue and the vas deferens was thin, its mucous membrane only slightly infolded The secondary sex characters were absent The hair growth of the male was very scant and resembled the

feminine distribution In old age the facial hair of the men resembled that frequently seen in old women The skin was pale puffy and wrinkled A marked panniculus adiposus distributed about the buttocks breasts trochanters and pubis with an accumulation of fat at the sides of the eyelids occurred At what age this adiposity was initiated is not definitely stated The epiphyses of the long bones remained ununited for a number of years after fusion should have occurred The pelvis and larynx were infantile Erection and coitus occurred in some individuals but was rare While the intelligence was normal there was considerable psychic disturbance and an indolent nature was characteristic

Castration in the juvenile age produces a more significant retardation of the entire genital system than the regression of these organs resulting from castration at a later age In the early castrate potency and libido are absent while in the late castrate there may be a slight retained libido producing mild erections in the male which fact led to the complete removal of the penis with the testicles in the harem watchers Pelikan reported a very early castrate in the male in whom the penis prostate and seminal vesicles remained infantile A Marie reports a case of a eunuch forty years old castrated in childhood who not only had sexual desire but also a peculiar erotic content attributed to the prostatic secretion The lack of sexuality and passion in the early castrate is associated with a classical psyche consisting of a shut in disposition and an absence of courage and aggression They have been described in the literature as deceitful unreliable crafty and merciless The intellect is not inferior History reveals that a number of the eunuchs had extraordinary capabilities Mobius observed however that very few of the true eunuchs ever rose to excellence as musical artists Among the physical characteristics of these individuals the laryngeal development with the child s soprano tone of voice is most interesting The laryngeal cartilage does not ossify at maturity the laminae thyroidi of the larynx encroach upon each other at wide angles and the prominentia laryngea is indistinct The dermal system is very much modified by early castration The hair of the head is unusually thick as compared with the facial and bodily hair The facial hair remains of the lanugal type or later in postadult life there appears a scant growth mostly on the lips and chin The axillary and suprapubic hair is sparse and the remainder of the body is comparatively free from hairiness The skin in early life is of a soft velvety character free from pigmentation Early in adult life it takes on senescent changes and often a yellowish brown coloring The features remain infantile with a decreased development of the maxillae tending to an anterior angulation of the face with recession of the lower jaw The orthodontial markings consist of enlarged upper medial incisors with small or absent lateral incisors Frequently all of the teeth are decreased in size sometimes miniature

The osseous changes consequent to decreased gonadal function during the period of skeletal growth do not include the short and flat bones which develop from their osseous nuclei The exaggerated long bone development is produced

by (1) late closure of the epiphyseal ends and (2) the presence of the hormones of osseous growth (anterior lobe pituitary and thyroid) The inverse proportions exist in all early hypergenital states, due to the early fusion of the epiphyses

The normal proportions for the various ages have been compiled by Stratz From composites of a large number of normal individuals of both sexes at different ages he produced the table given in Fig 3 It may be noted that at birth the upper measurement comprises five spaces as compared with the

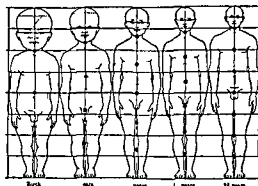


Fig 3 —Stratz composite picture of the normal proportions from birth to the age of twenty five Note that at birth the index of the upper and lower measurements is 5 3 at the adult age 4 4 (After Stratz Der Korper des Kindes 1904 64 Fig 42)

three spaces occupied by the lower measurement As the individual progresses to the age of twenty five, the upper measurement approaches and then equals the lower, the span then equaling the height This table also details the proportional distances of the head, eye line, navel etc , at different ages

It must be remembered that the statural proportions are dependent upon osseous growth and that the incretory imbalance must have occurred sometime before the adult age to have effected definite changes in the make up as represented by the comparative measurements The proportions of the individual are adaptable to diagnosis in only two endocrine conditions the preadult disorder of the anterior lobe hypophysis and of the gonads In order to visualize the contrast between these two types the reader is referred to Fig 4 a comparison of a case of pituitary tumor having neighborhood regional and general signs with a complete hypogonadism due to castration at the age of five This comparison is made at the adult age when normally the osseous system has completed its growth In the pituitarism (on the left) the upper measurement (90 cm) is much longer than the lower (76 cm) and the height (166 cm) exceeds the span (162 cm) The reverse of this is true in the hypogonadism (on the right) In the latter the upper measurement is much shorter than the lower and the span is

longer than the height The absence of hair distribution of the early castrate contrasts with the hypertrichosis of the pituitarism The infantile facies frail muscle system and hypoplastic genitalia of the castrate contrast with the hexagonal facial contour muscular and bony solidity and normal genital development of the pituitarism Fig 5 also depicts the contrast between the pituitary (anterior lobe deficiency) and gonad types

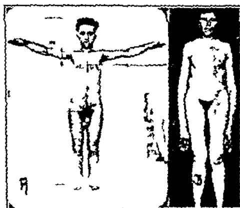


Fig 4 — Comparison of A a case of pituitary tumor with B a hypogonadism castrated at the age of five (both of adult age at time of comparison) Note the pituitary disproportion of A the upper measurement being longer than the lower the height longer than the span the inverse proportions obtaining in the early castrate B Also the hypertrichosis and normal genital development in A the absence of the characters in B (B is from J Tandler u S Grosz Die biol Grundlag d s kund G sch lechtschar published by J Springer Berlin)

The constancy of this skeletal configuration of early hypogonadism has been noted by Godard Pelikan Pittard Becker Lortet Hirsche Sellheim Tandler and Grosz and others Eunuchs of 200 cm (79 in) have been recorded The maximum growth in these cases usually occurs at about the age of maturity Osseous growth continues however several years after the age of twenty five when the centers of ossification normally are inactive The writer has observed the unfused epiphysis of the distal end of the femur as late as the age of twenty eight The long bone increase creates the appearance of a diminution of the flat bones For this reason there is a proportionately short vertebral column The pelvis in the male inclines to increased width and the genu resembles that of the female

The value of anthropometric studies relative to ductless gland function i

reduced after the adult age although these measurements may signify various functional activities or endocrine relationships antedating adult life The reciprocal function of endocrine glands throughout life may produce skeletal anomalies which must be carefully differentiated Overgrowth of the long bones must be accompanied by other signs of hypogonadism before the reproductive organs can be definitely incriminated Even in the preadult age, in order to de

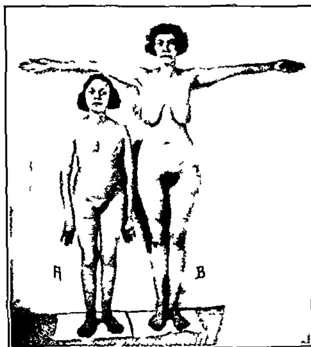


FIG 5 —Comparison of *A* anterior lobe hypopituitarism (Lorain Levi type) with *B* hypogonadism aged twenty and twenty one respectively Both had an amenorrhea Note the contrast in proportions *B* having comparatively a longer lower measurement and span and a shorter upper measurement than *A*

termine disproportion in growth from endocrine or other cause, the measurements must be compared with the standard for the individual s age (see Fig 3) Disproportionate measurements after the adult age indicate the existence of *some influence during* preadult life which has counteracted or *stimulated* epiphyseal activity or osseous growth Retardation or acceleration of osseous growth would act also upon the short and flat bones whose growth extends from their osseous nuclei The hypergenital states as macrogenitosomia suprarenal cortex disorder acromegaly, etc have an early union of the epiphyses with an overdevelopment of the short and flat bones, resulting in proportions opposite to those

of a hyposecretory state With this short stocky stature there is a precocity of genital development and function the causative factor in the early epiphyseal fusion

The osseous overdevelopment of gigantism supposedly a preadolescent hypersecretion of the anterior lobe of the hypophysis is difficult to explain Hyperfunction of the pituitary anterior lobe associated with a secondary hypergenitalism should produce early union of the epiphyses resulting in acromegaly instead of gigantism A plausible interpretation of gigantism in this regard is derived from clinical studies of these individuals While nearly all giants have a history of excessive inordinate sexuality clinical experience has revealed that this is of a transient duration of two or three years during preadult life soon changing into the opposite state as exhibited by a loss of libido and potency (partial or complete) accompanied by a diminished voluntary muscle tonus This state of preadult hypogonadism then would account for the disproportion of the eunuchoid giant Falta s theory that gigantism is a pluriglandular hypersecretion in which nearly all ductless glands are involved might also help to explain the long bone overgrowth and skeletal disproportion of an eunuchoid gigantism on the hypothesis that there is a relative hypogonadism as compared with other glandular activities in the complex On the same basis one might interpret the disproportion of acromegaly (upper measurement longer than lower height exceeding span) as due to a preadult hypergenitalism secondary to the anterior lobe hyperpituitarism rather than on the present accepted theory that the anterior lobe hyperfunction in this condition occurs in the post adult age after epiphyseal fusion thus affecting only the short and flat bone There is little likelihood however of mistaking the skeletal increase of hypogonadism for eunuchoid gigantism as the latter occurring oftener in the male has all of the objective signs of hypergenitalism whereas insufficiency of the sex glands is recognized by the genital aplasia and impotency as well as the differences in the secondary sexual characters

Postadolescent Variety — Gonadal insufficiency occurring between fifteen and twenty five years of age is designated as postadolescent hypogonadism (castrates and eunuchoids) The abnormal development of the long bones as described under preadolescent hypogonadism must also characterize postadolescent deficiency due to delayed epiphyseal fusion A second sign in some of the later postadolescent cases (particularly in the female) is a localized fat padding named by the writer from its circumscribed location a trochanteric adiposity (See Fig 6) It rarely develops in the early years of postadolescence In the male it may not appear before postadult life (See Fig 7) The chief regional hormonic sign after adolescence is the retarded state of the reproductive organs with absent or decreased function such as amenorrhea and frigidity in the female and loss of libido and potency in the male

In postadult hypogonadism the subjective symptoms refer more especially to the cardiovascular system while those of the preadult type consist largely

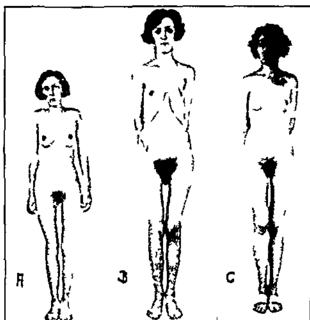


Fig 6 — Preadult female eunuchoid *A* aged fifteen *B* aged seventeen and *C* aged twenty one A had an amenorrhea of more than a year *B* short scanty periods and *C* an amenorrhea of two years and prolonged persistent vomiting Note the entire absence of adiposity in *A* slight trochanteric adiposity in *B* and beginning trochanteric deposition in *C* All have the enteroptotic abdomen and phthisical chest

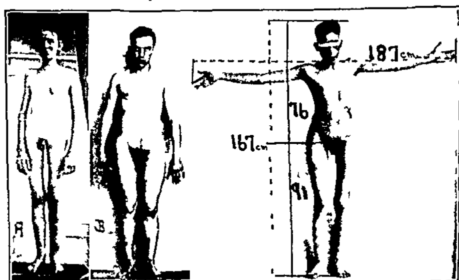


Fig 7 — Early male eunuchoid *A* aged eighteen *B* aged twenty four and *C* aged thirty Note their absence of adiposity and genital aplasia their classical disproportion illustrated in *C*

of nervous and gastrointestinal manifestations The nervous and vasomotor symptoms in the preadult castrate less marked in the eunuchoid consist of mental instability emotionalism hot flushes erythemas urticarias tachycardia palpitation and occasional syncope The gastrointestinal symptoms are more common in females and from the writer s observations are severer in eunuchoids than in castrates They vary from anorexia pyrosis distention and tympanites to regurgitation and prolonged intractable vomiting persistent in



Fig 8 — Early adult hypogonadism A was castrated at the age of seventeen *B* showed *eunuchoid* syn at eighteen Note the classical trochanteric adiposity without generalized adiposity at the age of twenty eight

some cases for years In one of the writer s cases a pernicious vomiting had been complained of for five years and was finally relieved by ovarian substitutional therapy This case had twice undergone abdominal exploration without discovery of any cause for her gastric distress

At this age the genital development and function are not the predominant feature of the female case *whereas in the male these symptoms form the greater part of the clinical picture The male under twenty five has relatively few nervous gastroenteric cardiovascular or general symptoms but he early seeks advice for his subnormal sexuality In the female at this age the symptom* complex refers chiefly to the above systems in conjunction with a fatigability sometimes attaining to a mental and physical exhaustion Such functional abnormalities as late maturity and the onset of an amenorrhea after a number of years of normal menstruation are often submerged in the other syndrome Many of these cases enter the marital state unconcerned with their imperfect menstrual function and innocent of their glandular defect with its sequence of frigidity and sterility

Adipose Hypogonadism

Hypogonadism after the age of twenty five, whether complete or partial, is separated into the early adult (before thirty three) and late adult (after thirty four) types In the late adult type a generalized adiposity is engrafted upon the earlier localized trochanteric padding which, as previously described, associated with a mild mammary and mons deposition, often occurs in the later postadolescent and early adult types (Fig 8) The generalized obesity of late

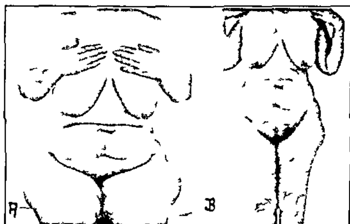


Fig 9 —Postadult castrate aged fifty two (two views A and B) Note the presence of a generalized engrafted upon a localized trochanteric adiposity

adult hypogonadism diffusely distributed over the body, simulating somewhat the obesity of myxedema, is seen in the female several years earlier than in the male It is not unusual to note its appearance in the female as early as twenty eight to thirty (Fig 9) In the male, however, the generalized adiposity is rarely observed before thirty four to thirty five (Fig 10) The writer has under observation a pronounced male eunuchoid who has attained the age of thirty four without developing either a localized or a general adiposity (Fig 7–C)

Obesity from other causes, endocrine or otherwise, in preadult and adult life must be excluded Juvenile or preadult (pituitary) obesity consisting of a girdle localization with a milder general panniculus can be readily differentiated from either gonadal or thyroid adiposity If we assume that hypogonadism does not produce a generalized obesity before twenty eight to thirty in the female or before thirty four in the male the age incidence excludes the sex organs as a factor in the earlier adiposity A hypothyroid obesity rarely exists in the first and second decades of life While overweight at birth is one of the cardinal signs of congenital hypothyroidism it usually does not persist after the second year

The adult myxedemas occur between thirty and forty rarely before thirty Occasionally a preadult hypothyroidism is noted usually associated with other signs to identify it as dorsal and supraclavicular padding and a definitely lowered basal metabolic rate In late adult life the association of a gonadal with a pituitary a thyroid or a combined pituitary and thyroid deficiency is not unusual In this instance the distribution of adiposity basal metabolism and early history are differential aids It may thus be stated that a large majority of adiposities at birth are thyroid in origin that juvenile obesity has a pituitary etiology [1] and that generalized gonadal adiposity does not occur before the fourth decade Without attempting to controvert the contentions of other authors the writer from studies of both castrates (70 cases) and eunuchoids (451 cases) has supported the basis that hypogonadism in the preadult age is unassociated with generalized adiposity and only in some cases *in the female is there a localized trochanteric adiposity*

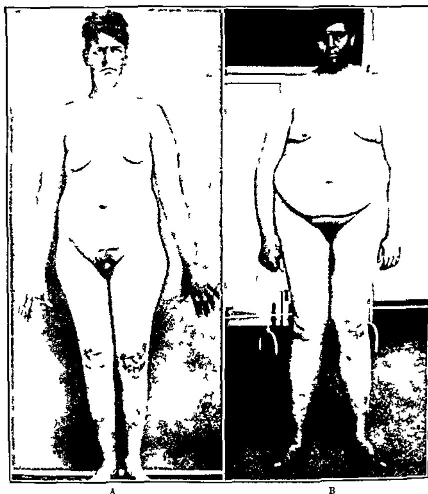
A suggestion of mammary adiposity in the male before the adult age is suspicious of a hypogonadism secondary to a pituitary deficiency involving the anterior lobe In the late adult age rapid hypertrophy of the mammae in the *male also indicates insufficiency of the sex organs Studies of this relationship* in male castrates have been more positive than in the female as mammary development in the latter is a constant secondary sex characteristic The relation of mammary function to pregnancy has also made this sign difficult of interpretation The distinction between adiposity of the mammae and *hypertrophy of the glandular tissue* is not definite enough to make the mammary adiposity an easily recognized sign nor is the function of the mammae in relation to the sex glands and other endocrine tissues clearly enough established On the contrary the trochanteric and mons adiposity seems to have a definite gonadal connection in both sexes

Hypogonadism initiated after the age of twenty five differs from preadult deficiency in its absence of osseous signs (described under pre and post *adolescent hypogonadism) as ossification has been accomplished under normal* influences prior to the disturbed secretion of the gonads

The early adult insufficiencies have practically the same cardiovascular nervous gastrointestinal and general symptoms as described under the post adolescent type In the female the psychic reaction due to a change from *potency to frigidity is much less than in the male In the former the vasomotor* and gastrointestinal signs are exaggerated in both the preadult and the early adult age whereas the functional nervous disturbances resulting in a sexual neurasthenia are the chief complaint of the latter Among the symptoms in the female is a marked fatigability and incapacity requiring increased effort for common place physical and mental activities Other symptoms (as described under the

[1] This is based on the earlier clinical (Engelbach) and recent anatomical (Abel Smith and Evans) theory of function of the posterior lobe of the hypophysis contrary to that advanced by the French school (Camus and Roussy)

previous type) vary from minor vasomotor manifestations to distressing functional cardiac involvement from anorexia to pernicious vomiting and from mild sensory disturbances to grave nervous states Rarely does the female complain pertinently of a tendency to amenorrhea or a subjective inhibition of function which varies from a slight aversion to the sexual act to a complete frigidity and sterility The male, with his more predominant sexual attitude, complains almost



A B

FIG 10 —Late adult hypogonad illustrating the general adiposity engrafted upon the localized trochanteric mons and mammary adiposity (right) *A* aged thirty six *B* aged forty three Note the pronounced trochanteric adiposity and female genu valgum of *B* the mammary adiposity and genital aplasia of both (*B* is published through courtesy of Dr Henry Enos Tuley Louisville Kentucky)

entirely of the genital signs as change in size and form of the genitalia diminished libido and potency, lack of reproductive power etc The female probably accommodates herself more readily to an asexual state and may welcome a less

ened function (amenorrhea) from fear of childbearing and the hardships incident to normal sexual activity

The susceptibility to respiratory infection particularly tuberculosis in the earlier type is not so characteristic of postadult hypogonadism probably at tributable to the resistance acquired during early life when the sex glands were normal in function While tuberculosis is not definitely selective as to age or type it is true that the so called phthisical or long narrow shallow chest is less immune to this disease The older writers believed that the mechanics of a chest so formed in preventing the aeration of the apices of the lungs were a predisposing factor in tuberculosis Modern students ver ed in the relation ship of the internal secretions to the general constitution and associating this thoracic contour with the osseous proportions of hypogonadism tend to the opinion that the deficient secretion from the sex organs has more to do with this susceptibility to pulmonary infection than has the actual configuration of the thorax This relationship can be applied also to the cardiovascular system The vertical character of the heart in these individuals frequently deemed ac countable for tachycardia palpitation and vasomotor disturbances as hot flushes and cold and blue extremities furnishes a clinical analogy We may regard simi larly the vertical position of the abdominal viscera in hypogonadism ordinarily described as the asthenic or the enteroptotic abdomen Considering the marked gastroenteric symptomatology often present in hypogonadism one can readily correlate the so called visceral displacement with the abdominal com plaints A summation of these various constitutional characters of preadolescent hypogonadism phthisical chest vertical heart enteroptosis with a disturbance of the autonomic nervous system completes the clinical complex formerly so vividly portrayed as primary functional nervous disease

An interesting phenomenon of late adult life particularly in the female is a hypertension sometimes present in the late castrate or eunuchoid type during the menopausal age Its endocrine relationship is confirmed by its immediate relief by ovarian substitution therapy after other treatment for hypertension has failed The writer has observed a woman in whom hypertension had ranged from 200 to 30 systolic for more than a year who had been on treatment con sisting of rest in bed elimination diet and medical and hydrotherapeutic agents After definite renal and cardiovascular lesion had been excluded and a menopausal etiology established the patient was encouraged to be up and around take a gen eral diet and discontinue therapy other than ovarian substance in large dosage by mouth and hypodermically The blood pressure dropped to 135 systolic within three days and for the following two years remained below 150 during which time she was permitted a general diet and normal activity

Aside from the general adiposity engrafted upon the localized deposition the symptoms of late adult hypogonadism are similar to those of the earlier adult type with possibly more implication of the cardiovascular system Symp toms such as hot flushes tachycardia dyspnea on effort and edema of the

previous type) vary from minor vasomotor manifestations to distressing functional cardiac involvement, from anorexia to pernicious vomiting and from mild sensory disturbances to grave nervous states Rarely does the female complain pertinently of a tendency to amenorrhea or a subjective inhibition of function which varies from a slight aversion to the sexual act to a complete frigidity and sterility The male, with his more predominant sexual attitude, complains almost

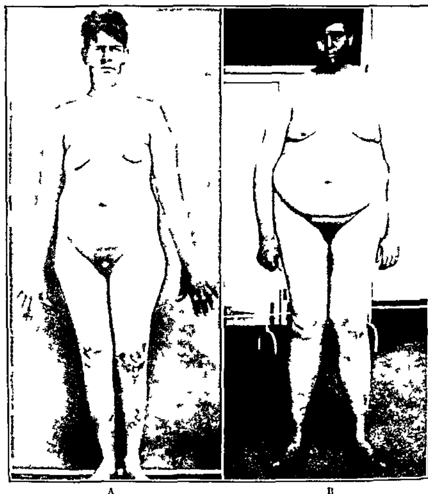


FIG 10 — Late adult hypogonad illustrating the general adiposity engrafted upon the localized trochanteric mons and mammary adiposity (right) *A* aged thirty six *B* aged forty three Note the pronounced trochanteric adiposity and female genu valgum of *B* the mammary adiposity and genital aplasia of both (*B* is published through courtesy of Dr Henry Enos Tuley Louisville Kentucky)

entirely of the genital signs as change in size and form of the genitalia diminished libido and potency lack of reproductive power etc The female probably accommodates herself more readily to an asexual state and may welcome a less

generative organs at a very early age in either sex The reader is referred to Fig 11, illustrating three cases in the male aged four six and eleven respectively and to Fig 1 The precocious genital development may be present at birth or have its inception in the first years of life progressing to adult size within a few months to several years In the male function of both the interstitial and spermatogenic tissues exists at this age and early masturbation and



FIG 11 — Macrogenitosomia A aged four B aged six and C aged eleven Note the hypergenitalism and unusual somatic development (C is the case of Dr Wm McKim Marriott Children's Hospital St Louis Missouri)

cohabitation are not uncommon In the female the first objective indication of hypergenitalism is the extremely early appearance of the menses In a case observed at the age of fourteen menstruation began in the first year of life and before the age of two the infant was having a menstrual flow equal in amount duration and regularity to that of her mother The most important character distinguishing these cases from suprarenal cortex or anterior lobe pituitary disorder is the absence of hypertrichosis In hypergenitalisms due to pituitary or to suprarenal cortex affection there is an abnormal bodily hair growth involving the face in the female This trichosis is not present in the pineal cases a circumstance which would isolate this specific hypergenitalism from those related to other ductless glandular dyscrasias

ankles are common Less frequent are signs referable to the nervous system, as migraine, general nervousness, emotionalism and fatigability Gastroenteric symptoms are not prevalent, as in the preadult disorders In late castrates symptoms referable to other systems are often absent, although in the majority a general obesity develops In castrates following the age of the menopause, the autonomic nervous system effects are not anticipated, yet in a few of these cases a less distinct symptomatology exists As the menopausal age varies, castration at that time of life must have a less characteristic clinical picture

Hypergonadism

Classification There are two general groups of hyperfunction of the gonads (1) primary (2) secondary In the first group the sex glands are primarily involved Secondary hypergenitalism is due to other influences usually the hormonic action of other ductless glands, as follows, (a) anterior lobe pituitary (b) pineal, (c) suprarenal cortex (d) thyroid

There is some doubt as to whether the entity of primary hypergonadism exists Primary tumors of the sex glands, particularly hydatid cysts frequently have been associated with hypersexuality sometime during the course Possibly most other cases are of secondary origin and not a pure hyperfunction of either ovaries or testicles With regard to the secondary hypergenitalisms, acromegaly is probably the most striking instance of those associated with anterior lobe pituitary disorder When of the aneoplastic type acromegaly usually has as a prominent feature a hypersexuality sometimes persisting from early life until the sixth or seventh decade In neoplastic acromegaly hypergenitalism is an early sign but frequently it soon reverts to the opposite state of activity probably due to destruction or to altered function of the anterior lobe of the hypophysis Gigantism is another illustration of transient gonadal hyperactivity secondary to anterior lobe hyperpituitarism Most of these cases have a hypersexuality of short duration, rarely enduring for more than a year or two during the stage of active osseous growth soon terminating in impotency and diminished libido The external gonadal secretion, as well as the internal apparently is involved in hypergonadism secondary to the hypophysis as evidenced by the *effect upon procreation and spermatogenesis The opposite or* decreased activity of the gonads is presented in anterior lobe hypopituitarism as illustrated by the Lorain Levi type, which in the female exhibits amenorrhea, frigidity and sterility and in the male genital aplasia and impotency In bilobar hypopituitarism concurrent involvement of the anterior and posterior lobes this decreased genital function is also present depending upon the amount of anterior lobe disorder

Pubertas praecox or macrogenitosomia is a classical demonstration of secondary hypergenitalism attributed by the writer to pineal disorder As is known, in these cases there is a precocity of development and function of the

which may persist for years This is noted more in the female than in the male Many of the nymphomanias are secondary hypergonadisms due to prolonged mild thyrotoxicosis In very severe states as exophthalmic goiter and pronounced hyperthyroidism the increased genital function often changes into a hyposexuality plausibly from the effect of the overwhelming intoxication in such conditions

Prognosis

The prognosis in anatomical malformations of the generative organs (aplasia cryptorchism hermaphroditism) and in hypergonadism requires little discussion The local genital malformation and associated general physical and nervous manifestations cannot be greatly altered

In the functional disorders the prognosis depends upon several factors (1) sex (2) age of onset (3) duration (4) degree of disorder (5) other ductless glands involved In castrates of either sex transplantation of the sex organs offers temporary abatement of the secondary symptomatology A case of procreation in a female castrate after ovarian transplantation has been reported (Morris) Although rarely attempted in the early male castrate transplantation of the organs should produce more positive result than in the late type The cryptorchism with retained secondary sexual characters attributed to a function of the interstitial substance of the gonads might also be benefited by organ transplantation if done at an early age The prognosis in cases in which the testicles remain in the abdomen must necessarily be more unfavorable than in those in which these organs are in the scrotum Surgery in the preadolescent age in these cases is therefore justified transferring the testicle from abdomen to scrotum for the purpose of inducing a more normal development and augmented effect from other treatment which might be considered at a later age There is no doubt that in the female castrate homotransplantation or replacement medication diminishes and sometimes averts many of the secondary symptoms If the very distressing signs referable to the nervous cardiovascular and gastrointestinal systems can be circumvented or relieved this treatment would seem more than justifiable As to whether the adipose and osseous changes might be influenced by treatment thus far there has not been adequate control to prove that these effects might be anticipated

The prognosis in eunuchoidism or partial gonadal insufficiency is comparatively favorable in the female but not so in the male To date no testicular substance on the market has had definite effect upon the regional or general symptomatology of male deficiency On the contrary positive therapeutic results have been obtained in the female (See Fig 13) These results however are dependent upon the age the duration of the disorder and the degree of involvement The younger the subject the earlier after the onset of the disorder the treatment is instituted and the milder the aberrant glandular function the more benefit may be anticipated relative to primary (genital) and secondary (other system) symptoms

As is known, hypernephroma or adenoma of the suprarenal cortex in the preadolescent age is productive of an unusual somatic development, in association with a hypergenitalism V Neugebauer, Marchand, Engelhardt, Fibiger Hepner and Ogston, and Meixner have described cases of this kind, controlled by autopsy or operation In some of the hypergenitalisms existing in pseudo hermaphroditism autopsy has revealed a hyperplasia of the suprarenal cortex

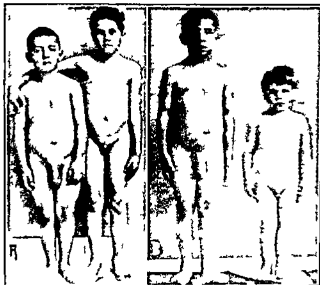


FIG 12 —*A* Compari on of a macrogenito omia aged four (left) with a normal boy aged thirteen *B* Compari *son of the ame ca e with a normal boy of his age (four)*

Classical cases of virilism and hirsutism have often been found to have tumor or hyperplasia of the suprarenal cortex The hypertrichosis as stated above is a significant sign particularly when it exists on the face in the female or occurs in the preadolescent male The duration of genital hyperfunction due to secondary involvement in these suprarenal cortex disorders varies In the majority it is not permanent in many of comparatively short duration, in which respect these cases simulate the secondary hypergonadism of gigantism Hyper trichosis is also recognized as related to anterior lobe pituitarism and in these cases must be distinguished from the hair growth of suprarenal cortex disorder by the associated hypophyseal signs Furthermore, the trichosis of pituitarism is much less pronounced than that of disturbed suprarenal cortex function The hair growth in preadolescent suprarenal cortex disorder is the predominant sign, whereas in hyperpituitarism it must be considered as a secondary or a tertiary manifestation, being overshadowed by other signs of primary pituitary disease

As to thyroid disorders a secondary genital hyperfunction may accompany hyperthyroidism The hyperthyroid states particularly during the initial stage in a constant mild hyperactivity sometimes have a secondary hypergonadism

stance ' *corpus luteum* (Frankel) *follicular hormone* (Allen and Doisy) and extract of stroma of the ovary have been used While there may be some difference in effect of corpus luteum follicular hormone stroma of the ovary and entire ovary in many cases differentiation of the indications for these preparations is difficult and for the general practitioner the substance from the entire ovary is probably most satisfactory particularly when attempt is made to correct constitutional symptoms or those pertaining to the secondary sexual characters Extracts from the entire ovary are administered in large dosage 1 to c c (15 to 30 minims) intramuscularly or in some instances intravenously in positive gonadal disorders Even larger doses frequently do not produce definite or measurable result due probably to the duration of the impaired function of the ovary Ovarian follicular fluid (Allen and Doisy) has been recommended in doses of 1 c c (15 minims) preferably given a few days following the menses (or the time for normal occurrence of the menses) After six to eight injections this extract should not be given until after the next menstrual period and subsequent series of treatments should depend upon the presence or absence of and the character of the menstruation The hypodermic preparations of corpus luteum and substance from the stroma of the ovary are administered in continuity at regular intervals in dosage of 1 to 2 c c (15 to 30 minims) depending upon the severity of the disorder and the clinical reaction In the experience of the writer a considerable number of these cases both castrate and eunuchoid have obtained undoubted effects as to both primary genital and secondary signs The cardiovascular gastrointestinal and nervous systemic symptoms are modified by substitutional therapy in these cases Symptoms such as tachycardia hot flushes headaches general nervousness anorexia nausea regurgitation and vomiting when a part of a definite gonadal complex are often completely relieved

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Treatment

The treatment for genital malformation can consist only in attempt at surgical correction of the anomalous condition In cryptorchism transference of the testicle to normal location or organ transplantation in selected cases might be considered

As to functional inactivities, in the writer s experience substitution by orchitic extracts in the male has been unsatisfactory Treatment relative to building up the general condition, increasing the weight and resistance, seems to be of more

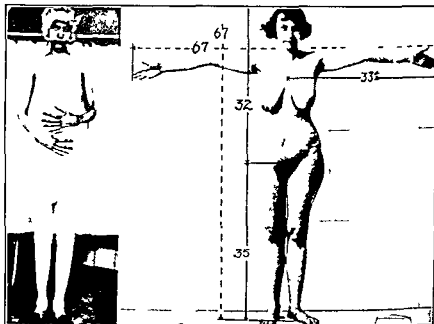


Fig 13 —Hypogonad *A* before and *B* after sub titution ovarian treatment with persi tent vomiting for five years (diagno is confirmed by exploratory opera tion) Weight before treatment 90 lbs after treatment 156 lbs Note the typi cal osseous disproportion

benefit to sexual impotency in the male than the so called hormone therapy Va sectomy and testicular transplants have been credited with a temporary rejuvena tion effect In selected cases in which no contraindications exist and the other systems of the body are comparatively free from senescent changes these might be considered The female castrates, however, should be given the benefit of early auto and homo transplantation In addition to or in lieu of this measure substitutional ovarian therapy should be administered hypodermically in large amount Whether the oral administration of the ordinary market ovarian prepa rations is efficacious is questioned The writer is of the opinion that most of these extracts when administered by mouth are practically impotent Ovarian sub-

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CHAPTER XVII

THE PINEAL BODY AND ITS DISORDERS

By ARTHUR GROLLMAN

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INTRODUCTION

Although the pineal body has attracted attention from ancient times its function if it has any remains an enigma The failure to demonstrate any effects from extracts derived from the gland or following its ablation as well as the more thorough anatomical and clinical data all suggest that it is a vestigial structure which no longer serves any function in the mammal The only clinical interest attached to the pineal body derives from the fact that it is occasionally the site of tumors which give rise to a characteristic syndrome seen also however in tumors and cysts originating in contiguous portions of the brain The fact that this syndrome is accompanied at times by precocity led to the view[10] that the gland normally plays a role in the determination of the time of sexual and somatic development However neither the clinical facts nor the experimental data support this view as will be shown subsequently

COMPARATIVE ANATOMY

The pineal gland is a derivative of only one of several glandular and sensory structures which in the lower invertebrates arise from the midbrain[32] A consideration of the comparative anatomy of these structures is of interest for the

light it throws on the probable function of the pineal as it occurs in man The pineal is a derivative of the epiphysial complex which gives rise to sensory as well as glandular structures The proximal portion of this complex gives rise to the pineal body the distal portion to the parapineal organ

Each of these components of the epiphysial complex consists of a body stalk and end vesicle, the development of which varies greatly throughout the vertebrates[53] In the cyclostomes petromyzon myxine bdellostoma, both the pineal and pineal organs are well developed the end vesicles forming eye like structures situated in a mid line depression of the skull These sensory organs are connected by nerve fibers to the ganglion habenulare and posterior commissure In the higher vertebrates the parapineal also gives rise to a sensory organ the parietal or third eye in certain saurians and in sphenodon a lizard like reptile of New Zealand In no existing form however is the parietal eye a functional organ of sight, nor can the pineal of the mammal be regarded as a vestige of a sensory organ[53]

There is a great variability in the structure of the pineal in various species Thus it is entirely absent or poorly developed in such dissimilar species as the sloth hump back whale anteater armadillo and daman[39] In this respect the pineal differs from other endocrine organs of undoubted function in which the constancy and similarity of the glands throughout almost the whole vertebrate series is striking[43] Moreover there is nothing in the reproductive development of the species mentioned above which would permit one to relate the presence or absence of the pineal to the sexual function

The histological appearance of the pineal also shows a remarkable variability In certain carnivora mole rodent echidna it is uniformly parenchymatous in structure In the bird also the pineal has a distinct glandular appearance with a follicular arrangement suggestive of secretory activity On the other hand in cattle the organ consists of fibrillar neuroglial tissue In man and the anthrapoid apes it consists of connective tissue septa separating islets of parenchyma in which are a dense web of fibrils ending in bulbous enlargements From an evolutionary standpoint man resembles the ophidia serpents in the state of development of the pineal having advanced less from the ancestral reptile than have such mammals as the cat beef or hedgehog[39]

From a comparative anatomical standpoint it is necessary to conclude that although the pineal may have a function in the bird and certain lower vertebrates it appears in man and most mammals to be only a vestige

Gross Anatomy of the Human Pineal

The pineal body in the human adult is a small reddish gray body about 8 mm long 6 mm wide and 4 mm in thickness, shaped like a fir cone It varies

in weight between 50 and 400 mgm average 170 Because of this conical shape it has been designated as the conarium (Greek κωνάριον) The term pineal also refers to its resemblance to a pine cone Its third designation the epiphysis refers to its position in relation to the hypophysis

The pineal body lies just beneath the splenium of the corpus callosum from which it is separated by the velum interpositum It is situated between the posterior ends of the thalami in a depression between the two superior colliculi of the corpora quadrigemina The free edge of the tentorium cerebelli lies below and behind It is attached to the roof of the third venticle by a hollow stalk which projects from the base of the gland and is directed backward The stalk is divided into two laminas by the pineal recess of the third ventricle The tela chorioidea of the third ventricle separates the pineal from the splenium of the corpus callosum and envelops the gland Inferiorly the pineal lies in relation to the corpora quadrigemina posteriorly to the anterior vermis of the cerebellum and laterally at the base it is in close proximity to the optic thalami It is these surrounding structures of the pineal body which are compressed by tumors arising in the pineal and give rise to the syndrome to be described later

The pineal lies close to the communication between the third and fourth ventricles and to the cerebellar and pontine spaces and is in direct contact with the large venous channels that drain the central region of the brain

The deep cerebral veins which run in the velum interpositum unite just about the tip of the gland to form the large vein of Galen Enlargement of the pineal when it is the site of a tumor thus rapidly induces hydrocephalus by blockage of the aqueduct of Sylvius and may also compress the large veins in contact with it

Embryology and Histology

The pineal body appears in the human embryo at the beginning of the second month as a simple layer of ependymal cells projecting from the posterior part of the roof of the diencephalon As this cell mass enlarges it is divided by an evagination from the wall of the third ventricle to form a diverticulum which gradually recedes and disappears by the sixth month of fetal life According to Krabbe[26] the mass of cells which lies anteriorly to the diverticulum actually represents a second anlage of the gland and is a derivative of the parapineal organ of the epiphysial complex

By the end of the third month of fetal life the cells have formed a structure consisting of small tubules giving it the appearance of a glandular organ[10] Mesenchymal elements penetrate between these tubules and give rise to connective tissue septa and small cells resembling lymphocytes The cells of the tubules multiply their lumens disappear and the organ by the sixth month of fetal life consists of large light parenchymal cells surrounded by strands of

small deeply staining cells which give the organ a characteristic mosaic appearance. This is the histological appearance of the gland at birth.[1]

The large parenchymal cells are accepted generally as being of nervous origin. The histogenesis of the small cells is disputed. Horrax and Bailey[20] regard



Fig. 1. Structure of normal pineal body. Hortega's method for pineal parenchyma. × 700. Typical pineal parenchymal cells ending in bulbous terminals. (From Horrax and Bailey, Arch. Neur. and Psychiat., 1928, xix, 394.)

them as glial cells of neuroectodermal origin; Globus and Gilbert[21] as mesenchymal in origin and differentiating into the fibrous tissue septa which replace the small cells after birth.

Following birth there is a gradual diminution in the number of the small

darkly staining cells which virtually disappear by the end of the ninth postnatal month During this same period *the parenchymal cells form protoplasmic processes* which extend towards the connective tissue septa and blood vessels where they end in bulbs[31] (Fig 1)

With advancing age there is little change in the appearance of the gland except for an increase in the connective tissue septa and the appearance of focal areas of calcification which may be evident as early as the second year of life In the adult there is at times an almost complete disappearance of the epithelial cells and their replacement by calcareous granules acervulus brain sand of varying size which have a mammillated structure corpora arenacea Other changes of a regressive character are hyalinization fibrosis and the formation of cysts Despite this degenerative process a few cells remain which structurally at least appear to be potentially functional It is this calcification of the gland which renders it demonstrable often in x rays of the skull and makes it possible to infer from its posterior displacement the presence of a subtentorial tumor

The granules present in the parenchymal cells have been variously interpreted as evidence of secretory activity as blepharoblasts as retinal pigments and as signs of involution It is impossible to conclude from its histological structure whether the pineal is a functional organ showing secretory activity

Physiology

Attempts to discover the function of the pineal gland have been made by studying the effects of feeding and implanting pineal tissue by injecting extracts derived from the gland and by extirpating the organ in the experimental animal The immediate effects which follow the injection of pineal extracts are evanescent and resemble those seen following the injection of crude tissue extracts generally The claim that long continued injection of these extracts leads to retardation of sexual maturity and growth probably also is of no significance Any crude glandular extract particularly if contaminated with noxious chemicals such as traces of picric acid will induce similar effects and hence the above mentioned experiments are without significance insofar as the function of the pineal body is concerned[5]

The implantation of pineal tissue or injection of pineal extracts has been claimed also to exert gonadotropic as well as antigonadotropic effects[17] Because of the conflicting data and non specific nature of these reactions the conclusions reached are not convincing The same may be said of the effects of pineal extracts on glycogen storage in the liver of the fowl[1] The effects of feeding pineal tissue or extracts to tadpoles and fowls also are conflicting[10] The best available evidence would indicate that these are without effect Nor is there any valid data to support the claims that pineal preparations are of any value in the diverse

clinical conditions nocturnal enuresis precocious puberty schizophrenia, menstrual disturbances for which they have been used

The earlier investigators of the effects of ablation of the pineal claimed to demonstrate accelerated growth of the body and precocious maturity of the reproductive organs However they failed to take into account the normal variations in the age of puberty and rate of growth nor because of the high mortality of the operation were sufficient animals used to allow one to draw any statistically valid conclusion Anderson and Wolf[1] have shown the inadequacy of the experiments carried out by earlier workers on the rat, guinea pig rabbit dog, chick and frog The more recent results of Davis and Martin[11] on the cat are open to similar objections In the rat pinealectomy during the first days following birth fails to influence the rate of growth the age of puberty the weights of the endocrine organs and gonads or the estrous cycle[1] Pinealectomy in successive generations of rats likewise fails to result in any demonstrable effects[16 50]

Physiological experiments thus have failed to demonstrate any function attributable to the pineal gland The claim that the gland controls the secretion of the spinal fluid also lacks substantial support[14]

Tumors of the Pineal Region

The pineal body is of clinical interest because it is sometimes the site of tumors which give rise to a characteristic syndrome which may be designated as the pineal syndrome Instances of chronic infection tuberculosis syphilis and hemorrhage of the gland have been noted also[6] but these are rare and of no practical clinical importance The nature of the primary tumors arising in the gland varies but since most of the symptoms to which they give rise result from pressure effects on surrounding tissues the pineal syndrome is independent of the histological structure of the primary growth

Cases of pineal tumor are rare representing only about 1 5 per cent of all intracranial new growths In 1911 Pearce Bailey and Jolliffe[5] collected 60 cases from the world s literature By 1927 Haldeman[27] was able to review 113 cases while Bing Globus and Simon[7] in 1938 brought the total of reported cases to 177 The 10 cases reported by Baggenstoss and Love[3], the 7 of Russell and Sachs[43] and the individual case reports which have appeared periodically[8 9 1 5 43 54] bring the total number of cases in the world literature to slightly over 200

Of the 58 cases of pinealoma collected and analyzed by Russell and Sachs[43] 28 occurred in young adults between the ages of 15 and 25 years 17 in persons at or under 15 years and 13 in adults over the age of 25 The 3 youngest patient were 2 years of age the oldest was age 50 Only 5 of the 58 patients were females Practically all of the reported teratomata of the pineal have occurred in children

or young adults The average age of the 19 patients with embryonal tumors collected by Bochner and Scarff[8] was 12 years only one patient aged 7 being over 19 years of age Cysts on the other hand practically always have occurred in adults

Pinealoma is much less common in the female than in the male Thus only 5 of the 58 cases collected by Russell and Sachs[45] were females Of the 9 embryonal tumors collected by Bochner and Scarff[8] only one occurred in a female Other tumors of the pineal are also four or five times as common in the male as in the female

Pathology

The pineal gives rise to tumors of such diverse cellular types and unusual architecture that there is often considerable uncertainty as to their classification

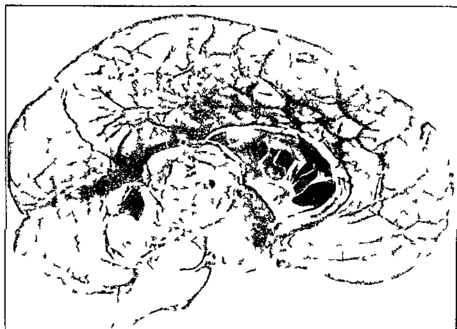


Fig 2 Pineal teratoma shown in compression of surrounding structures with dilatation of lateral and third ventricles (From Horrax and Bailey Arch Neur and Psychiat 1925 xi 423)

Neuropathologists often disagree as to the correct nomenclature with which a given tumor is to be designated because of the difficulty in determining its histogenesis The most common primary tumor of the pineal is the pinealoma (Fig 2) a term introduced by Krabbe[37] to designate tumors arising from the parenchyma

tous cells In addition the pineal is the site of origin of teratomata (Fig 3), teratoid tumors a variety of tumors originating from nerve cells, cysts and rarely, sarcoma and chorionepithelioma

Only such tumors as originate from the parenchymatous pineal cells should be designated as pinealomas These tumors show a great diversity in their size and histological structure The most differentiated ones resemble microscopically the pineal of the new born showing the characteristic mosaic structure with cords



Fig 3 Typical pinealoma of quadrilateral shape Note the marked compression of cerebellum dilation of the third ventricle and demarcation of tumor from surrounding structures (From Horrax and Bailey Arch Neur and Psychiat 1925 xiii 423)

of small lymphocytic like cells surrounding the lighter and larger parenchymal cells (Fig 4) However deviations from this histological pattern are common The mosaic structure may be absent and the small as well as the parenchymal cells may show great variability The pinealoma representing as it does an autonomous new growth of a whole tissue is a unique example of an autochthonous teratoid type of tumor comparable to chorioma and thymoma According to Russell and Sachs[18] the presence of the two types of cells is essential for the designation of a tumor as a pinealoma Globus and Silbert[24], on the other hand, consider certain tumors containing only one type of cell as pinealoma which they

believe originate from the pineal cells present in the embryo before differentiation into two cell types has occurred

Dorothy Russell recently has presented evidence pointing to the conclusion that pinealoma is an atypical teratoma rather than an autochthonous derivative of the pineal parenchymal cells This view would explain the occurrence of so-called ectopic pinealomas 11 of which are on record, in which typical pineal tumors occur in the brain at sites distant from the pineal body As Russell points out the so called pinealoma differs mor phologically from normal paren chymal pineal tissue in that the nuclei of the large spheroidal cells in this tumor contain one or more conspicuous eosinophilic nucleoli their cytoplasm contains no gran ules they lack the bulbou endings and show little affinity for silver carbonate all of which are so characteristic of the normal pineal cell The so-called pinealoma re sembles closely the spheroidal cell carcinoma of the testis[8] which is regarded as an atypical teratoma Russell[47] does not deny the exist ence of true pinealomas that i tumors arising from the pineal parenchymal tissue and describes a case conforming to this designation She considers the so-called spongioblastic pinealomas described by Horrax and Bailey[31] as probably representin such true pinealomas



FIG 4 Microscopic appearance of pinea loma Hematoxylin and eosin stain x 80 Note the large pineal parenchymal cells and the small lymphoid cell in the connective tissue reticulum (From Horrax and Bailey Arch. Neur and Psychiat 19 5 xiii 4 3)

Typical teratomas of the pineal are rare comprising about 10 per cent of pineal tumors Only 13 proven cases could be collected by Bochner and Scarff[3] in 1938 In addition these authors found 4 cases which they considered as tera toid that is containing only ectodermal and mesodermal elements instead of elements of all three germinal layers as in the teratoma

The other common tumors occurring in the region of the pineal body are de rived from neuroglial tissue glioblastoma or spongioblastoma multiforme ganglionic elements ganglioneuroma mural derivatives of the third ventricle

tous cells In addition, the pineal is the site of origin of teratomata (Fig 3), teratoid tumors a variety of tumors originating from nerve cells, cysts and rarely, sarcoma and chorionepithelioma

Only such tumors as originate *from the parenchymatous pineal cells should* be designated as pinealomas These tumors show a great diversity in their size and histological structure The most differentiated ones resemble microscopically the pineal of the new born showing the characteristic mosaic structure with cords



FIG 3 Typical pinealoma of quadrilateral shape Note the marked compression of cerebellum dilation of the third ventricle and demarcation of tumor from surrounding structures (From Horrax and Bailey Arch Neur and Psychiat 1925 xiii 423)

of small lymphocytic like cells surrounding the lighter and larger parenchymal cells (Fig 4) However deviations from this histological pattern are common The mosaic structure may be absent and the small as well as the parenchymal cells may show great variability The pinealoma representing as it does an autonomous new growth of a whole tissue is a unique example of an autochthonous teratoid type of tumor comparable to chorioma and thymoma According to Russell and Sachs[48] the presence of the two types of cells is essential for the designation of a tumor as a pinealoma Globus and Silbert[4] on the other hand, consider certain tumors containing only one type of cell as pinealoma, which they

Pressure on the corpora quadrigemina gives rise to certain pathognomonic eye signs. Paralysis of upward gaze, loss of conjugate movements of the eyeballs upward, Parinaud's syndrome, results from pressure on the pretectal region in front of the superior colliculi. Frequently there is also bilateral ptosis. Just beneath the pineal body are the fibers which transmit the light reflex so that the pressure on the quadrigeminal plate results in Argyll Robertson pupils without, however, the myosis and irregularity of the pupils seen in neurosyphilis. Pressure on the oculomotor apparatus or nuclei in the midbrain gives rise to paralysis of the ocular muscles and double vision. Skew deviation of the eyeballs is observed frequently. The combination of the oculomotor phenomena with other evidence of a brain stem lesion is practically pathognomonic of a pineal tumor[1].

As the tumor enlarges it may compress also the lateral lemnisci and medial geniculate bodies, resulting in auditory disturbances. These are usually bilateral[1] but may be much more pronounced on one side[8]. Irritation of these fibers may give rise to auditory hallucinations. These acoustic difficulties with ultimate partial or complete deafness have been noted in about a third of the cases. If the subthalamic nuclei or the corpora luysii are involved, choreiform movements occur, but this is rare.

The pressure of the internal hydrocephalus may affect distant hypothalamic centers. This gives rise to disturbances in the metabolic and vegetative functions and manifests itself in somnolence, diabetes insipidus, polyphagia, adiposity and precocious sexual development. This pressure effect may cause also enlargement and destruction of the dorsum sellae of the pituitary and give rise to symptoms of pituitary insufficiency.

The symptom sometimes present in cases of tumor of the pineal which has attracted the greatest interest and emphasis is the precocious somatic and sexual development (Fig. 5) designated by Pellizzi[14] as macrogenitosomia praecox and sometimes referred to as Pellizzi's syndrome. It is the occurrence of this symptom which suggested that the pineal secreted a hormone which induced somatic and gonadotropic maturity, or that it normally inhibited the advent of puberty[40]. As a matter of fact precocity is present only exceptionally in tumors of the pineal. Thus in the cases of pinealoma collected by Russell and Sachs[43] precocious puberty was observed in only 3 of the 17 patients who were 15 years of age or younger. On the other hand 9 of the 19 cases of embryonal tumors collected by Bochner and Scarff[5] manifested the Pellizzi syndrome. Of the 177 cases of pineal neoplasm collected by Bing, Globus and Simon[7] pubertas praecox was present in only 21.

If the pubertas praecox observed in pineal tumors be due to the secretion of a hormone, it would be anticipated that this condition would be more common in pinealoma than in other primary tumors of the pineal which usually destroy the pineal parenchyma. This, however, is not the case and many pinealomas

glioma, spongioblastoma unipolare astrocytoma ependymoma, or fibrovascular cells sarcoma and hemangioma Mixtures of these tumors also have been described as ganglioglioneuroma, neuroglioma ependymale etc

Cysts arising from the vestigial pineal recess also occasionally give rise to new growths and the pineal syndrome There are only two instances of chorion ephithelioma of the pineal in the literature[9, 13]

Many of the pineal tumors are slow growing well circumscribed tumors Others grow fairly rapidly and invade the surrounding tissues

Distant metastasis from neoplasms of the pineal body are rare Baggenstoss and Love[1] observed 2 cases with metastases to other parts of the central nervous system and were able to find only 5 other cases in the literature In 3 of these the metastasis was to the spinal cord In 5 cases there was metastasis to the region of the third ventricle with diabetes insipidus In most cases the tumors invade the surrounding brain tissue, the wall of the ventricular system and the subarachnoid space

Symptomatology

The symptoms and signs produced by tumors of the pineal may be divided into three categories (1) those due to increased intracranial pressure, (2) those due to pressure on contiguous structures and (3) vegetative disorders including macrogenitosomia praecox, induced by hypothalamic dysfunction

The earliest symptoms induced by pineal tumors result from increased intracranial pressure The position of the gland is such that new growths in this area occlude the aqueduct of Sylvius giving rise to hydrocephalus and dilatation of the lateral ventricles (Figs 2 and 3) The increased intracranial pressure induces the general symptoms of any space occupying lesion headache vomiting and failing vision, which are the first symptoms noted by the patient At times the tumor may act as a ball valve with intermittent occlusion of the aqueduct resulting in periodic attacks with relief in the intervening periods Headache is usually the earliest and most troublesome symptom It is usually occipital at first but may be frontal and ultimately becomes diffuse Papillary edema of 4 to 6 diopters is a common early finding observed in 90 per cent of the cases

As the primary growth enlarges it presses on the cerebellum and on the superior colliculi of the corpora quadrigemina (Figs 2 and 3) Pressure on the former may give increased muscle tone weakness without paralysis of the extremities increased tendon reflexes nystagamus and disturbances of equilibrium and gait suggestive of a cerebellar tumor These effects are due to pressure on the sensorimotor tracts the cerebellum or its midbrain connections Cerebellar asynergia and adiadokinesis are observed sometimes Ankle clonus and a positive Babinski sign also are encountered occasionally

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as we have seen are not accompanied by this syndrome Since tumors on the other hand which completely destroy the pineal also give rise to precocity, it is impossible to incriminate the pineal tissue per se as the cause of the disorder It is more logical to attribute the development of pubertas praecox in pineal tumors to the pressure exerted by these neoplasms on the contiguous hypothalamic centers[3] In conformity with this view is the fact that similar precocity is



Fig 5 Patient R B P aged three years $6\frac{1}{2}$ inches above normal height external genitalia somewhat large for his age (*From Horrax and Bailey Arch Neur and Psychiat* 1925 xiii 423)

observed in other intracranial lesions which in no way encroach on the pineal[10] for example in tumors of the floor of the third ventricle in tuberous sclerosis in hydrocephalus[15], in ventricular cysts[18] in ependymoglioma of the mammillo-tuberal area[29] in glioma of the midbrain[49], in inflammatory lesions of the base of the brain[19 51] and in tumors of the hypothalamus[57] All of these cerebral involvements induce true *precocity as do also the tumors of the* pineal in contrast to the androgenic tumors of the adrenal which do not induce ovulation and spermatogenesis but only the premature development of secondary sexual characters[5]

An alternative hypothesis to explain the occurrence of pubertas praecox in

pineal tumors is to assume as first suggested by Krabbe[13] that these growths *induce their effects because of the presence of gonadotropic teratomatous elements* This interpretation is particularly appropriate if we accept Russell's[17] view as to the teratomatous nature of so called pinealoma It would account also for the greater frequency of precocious puberty in cases of typical teratoma of the pineal as compared to other pineal neoplasms Further support for this view is the presence of gonadotropic hormone in the urine in some cases of pineal tumor[13] Further studies with more exact determinations of the nature of the *hormones present and their correlation with the clinical findings are desirable* It would appear most likely that the pubertas praecox observed in pineal tumors may originate both as a result of the secretion of specific gonadotropic or androgenic *hormones as well as a result of pressure on hypothalamic centers*

It is of interest that pubertas praecox resulting from pineal tumors is relatively rare in the female Thus among the 21 cases of pubertas praecox due to pineal tumor collected by Bing Globus and Simon[7] only one was in a female Of 13 cases of pubertas praecox with extensive involvement of the brain only one was a female On the other hand pubertas praecox resulting from other central nervous system involvements are not uncommon in the female Thus Gross[6] *has reported a case of astrocytic hamartoma in a female infant age 2 with* pubertas praecox Flicker[18] observed the condition in a female infant with a cyst in the third ventricle which compressed the epithalamus thalamus hypothalamus *and adjacent structures and gave rise to the typical pineal syndrome* In Ford and Guild's[19] 3 cases of pubertas praecox following encephalomyelitis were females In these cases one has to assume that the observed changes in the reproductive organs are secondary *to changes in the hypothalamus*

Genital dystrophy also has been encountered occasionally in pineal tumors[3] due presumably to the effect of compression on the pituitary

Differential Diagnosis

The diagnosis of a primary tumor of the pineal is not difficult when the growth has advanced and exerted pressure on the quadrigeminal body At this time the pathognomonic eye signs inability to gaze upward bilateral ptosis the skew deviation in the presence of signs of increased intracranial pressure and the *absence of localizing signs are indicative of the presence of a tumor in the pineal* or in the vicinity of this gland

During the earlier stages of the disorder when the only symptoms and signs *are indicative of increased intracranial pressure with perhaps evidence of vegeta*tive disorders due to pressure on the hypothalamic centers localization is impossible by clinical observation alone and requires ventriculography However the early appearance *of signs of increased intracranial pressure differentiates the e*

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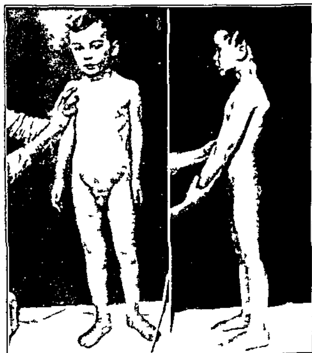


FIG 5 Patient R B P aged three years 6½ inches above normal height external genitalia somewhat large for his age (From Horrax and Bailey Arch Neur and Psychiat 1925 xiii 423)

observed in other intracranial lesions which in no way encroach on the pineal[70] for example in tumors of the floor of the third ventricle in tuberous sclerosis in hydrocephalus[15] in ventricular cysts[18] in ependymoglioma of the mammillo-tuberal area[29] in glioma of the midbrain[49] in inflammatory lesions of the base of the brain[19 51] and in tumors of the hypothalamus[57] All of these cerebral involvements induce true precocity as do also the tumors of the pineal in contrast to the androgenic tumors of the adrenal which do not induce ovulation and spermatogenesis but only the premature development of secondary sexual characters[5]

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Operative removal of pineal tumors is followed by a very stormy course for a week or ten days due apparently to the acute edema induced by manipulation at the time of the operation and the unavoidable necessity of interfering with normal venous drainage to avoid bleeding For this reason frequent tappings of the ventricle are necessary postoperatively Permanent bilateral homonymous hemianopia also at times has been a postoperative complication Dandy[1] attributes this to pressure on the cuneus at the time of operation Harris and Cairns[8] suggest that it is due to severing the posterior occipital veins which interferes with the circulation through the visual areas

Paraphysial Cysts

Although not involving the pineal body proper attention may be called here also to the paraphysial cysts of the third ventricle[16] These arise from the paraphysis a phylogenetically old formation arising in the midline of the rostral portion of the roof of the third ventricle The paraphysis is a rudimentary vestige of the parapineal body which may be demonstrated as a vesicular formation in the human embryo[38] Seventeen cases of successful removal of cysts arising in this vestigial gland are now on record[16] These cysts are small benign encapsulated tumors which occupy the third ventricle Their presence is demonstrable by cerebral pneumography Violent headache influenced by posture is the most significant symptom caused by these cysts The technique for their surgical removal has been described recently by Weinberger and Boshes[6]

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tumors from growths lower in the brain stem in which the initial symptoms usually are those resulting from involvement of the cranial nerves The signs of cerebellar dysfunction noted early often suggests a cerebellar lesion, and many cases are operated on with this mistaken diagnosis

In suspected cases of pineal tumor ventriculography will show the symmetrical bilateral dilatation of the lateral and third ventricles This procedure may show also a filling defect in the posterior part of the third ventricle and obliteration of the suprapineal recess The presence of a calcified shadow in the pineal area particularly in young children may afford objective evidence also of the existence of a pineal tumor[1]

Prognosis and Treatment

Tumors of the pineal, when left untreated lead to early blindness and death usually within a few months Their operative removal although obviously desirable is difficult and attended by a high mortality Conservative treatment consists in a subtemporal decompression followed by deep x ray therapy Most of the pineal tumors are radiosensitive and these measures relieve the headaches and other effects of increased intracranial pressure and save or improve the vision for many months Horrax and Daniels[33] reported 4 cases treated conservatively by the above methods with success in 3, making it possible for the patients to return to a useful life for periods of $1\frac{1}{2}$ to $2\frac{1}{2}$ years

Operative procedures for removing pineal tumors have been described by Dandy[11] and Van Wagenen[5] In Dandy's operation the tumor is approached from the occipital area After separating the right cerebral hemisphere from the falx the corpus callosum is split and the posterior part of the right cerebral hemisphere is resected if necessary to give a good exposure In Van Wagenen's procedure the tumor is approached through the dilated lateral ventricles Dandy[1] has reported 3 survivals following a seemingly total extirpation Russell and Sachs[48] cite 3 cases operated on successfully by Dandy German and Horrax with a 5 year survival without recurrence In another case operated on by Horrax the tumor was incompletely removed and the patient was treated with x ray but died following an attempt at radical removal of the recurrent tumor 8 years following the first operation Van Wagenen[50] reported a patient who was apparently normal 15 months postoperatively and Pratt and Brooks[46] excised successfully a glioma of the pineal from a 25 year old woman who showed no evidence of recurrence $3\frac{1}{2}$ years later Harris and Cairns [8] patient showed a recurrence 9 months postoperatively but was improved by subsequent irradiation

The combination of operative removal followed by irradiation thus apparently offers the best probability of at least a temporary remission and the possibility of an occasional cure Because of the high mortality attendant on the operation the prognosis is at best, very poor

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CHAPTER XVIII

FUNCTIONAL GYNECOLOGICAL DISEASES

By EMIL NOVAK

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INTRODUCTION

Specialism as it exists today *not only* justifies but also necessitates concentration of study in one field or another of medical practice. It *does not however excuse a lack of reasonable* familiarity *with other* fields. The broadest of all the specialties is that of the internist, blanketing as it does *practically all the others*. *Into the diagnostic work of* the internist gynecological problems often obtrude themselves. At one time these were concerned chiefly with definite pathological lesions of one sort or another which might involve the pelvic organs. For example adnexal inflammation very well might be the cause of lower abdominal pain, a uterine myoma or carcinoma very well might be responsible for secondary anemia and so on.

The whole complexion of gynecological practice, however, has changed within the past quarter of a century and especially within the past decade or so because of the enormous advances which have been made in our knowledge of reproductive physiology. No longer is gynecology to be looked upon as a mere subdivision of surgery, as many were inclined formerly to regard it. Indeed every competent gynecologist will agree that only a comparatively small proportion of all cases coming under study will call for any surgical procedure as a part of therapy.

Pretty much all of the great new mass of knowledge concerning the physiology of the reproductive processes pertains to their endocrinology. It is because of the intensiveness with which the problem of reproductive physiology has been, and still is being studied and because of the direct applicability of many of the newly discovered facts to the interpretation of clinical problems, that interest in endocrinology has been developed more highly among gynecologists than among specialists in almost any other field. Endocrinology now is woven inextricably into the fibre of medical practice in all its aspects and the very nature of endocrines and endocrine disorders makes impossible any sharp regional limitation in the study of the subject. Moreover the slowly developing but persistent attempts at organotherapy in all sorts of disorders often involve the use of various sex hormones even in the treatment of non-gynecological conditions. Unless the internist is familiar with at least the elements of reproductive endocrinology, therefore he can scarcely have an intelligent concept of the various gynecological endocrinopathies of the frequent distant or constitutional effects of such endocrinopathies or of the gynecological manifestations of disturbances originating in endocrine glands other than the gonads themselves.

The rational plan for this brief chapter therefore would seem to be (1) a resume of the endocrinology of the menstrual cycle and (2) a discussion of the more important gynecological endocrinopathies and their treatment. This will include a consideration of the sex hormone products used most frequently in the treatment of both gynecological and non-gynecological disorders.

The Endocrinology of the Menstrual Cycle

The concept of ovarian endocrine function which prevailed in the early years of the present century was very simple predicating merely

a single internal secretion which in some way was responsible for menstruation With the discovery by Fraenkel (1903) of the endocrine activity of the corpus luteum there were many who assumed that this structure was the sole source of the ovarian secretion As a matter of fact, it was not until the discovery of the follicular hormone by Allen and Doisy in 19 , that we could separate the endocrine principle of the ovary rather sharply into two separate hormones one produced by the growing follicle the other by the corpus luteum This new knowledge fitted in very smoothly with what had been learned in the meantime as to the histological sequence of events during the cycle

Beginning just after a menstrual period a considerable group of follicles begins to mature and incidentally to produce increasing amounts of the follicle hormone which formerly was known by various names viz estrone estrin female sex hormone theelin folliculin menformon etc It is known to occur in various derivative forms and to the whole group the generic designation of estrogens is applied Only one of the group of follicles as a rule reaches full maturity and ovulates usually at about the mid interval between periods The other follicles are blighted at various phases through the process known as atresia folliculi

After ovulation the collapsed follicle begins a second or corpus luteum phase of development rising like a phoenix from the ruins of the follicle and progressing to an acme which is reached probably five or six days before the onset of the next period During its growth it continues to secrete estrogen but in addition it produces a second and more characteristic corpus luteum hormone known as progesterone

What effects are exerted by these two hormones upon the uterus? Estrogen may be looked upon as a growth hormone possessing a highly selective effect upon genital mucous membranes The endometrium therefore undergoes a steadily increasing developmental advance from the end of one period to the beginning of the next In addition estrogen has a less conspicuous developmental effect upon the musculature and apparently is responsible for the normal rhythmic contractility of the latter

Progesterone on the other hand becomes operative only after ovulation and is responsible for the secretory activity of the gland epithelium which becomes increasingly apparent after the formation of the corpus luteum and which apparently is essential to the implantation of the egg in the event of this having been fertilized It probably exerts an inhibitory effect upon the rhythmic contractility of the uterus although on this point some difference of opinion has arisen among recent investigators It has been established through the work of Venning and Browne

and others that progesterone is excreted through the urine in the forms of pregnanediol This fact has been put to practical clinical use in the study of various disturbances of menstruation and pregnancy

From what little has been said already, it is clear that no amount of estrogen is, in itself, capable of producing in the uterus the same changes which characterize the normal cycle Both ovarian hormones, acting in sequence, are essential for this This obviously has a bearing on the treatment of amenorrhea A second point, which should be stressed, is that when the ovarian hormones are used in the treatment of amenorrhea, their effect is purely substitutional, for it is well established that they have no stimulating effect on the ovaries, i e, they are not capable of starting the ovarian machinery

While ovulation occurs most often between the tenth and seventeenth days of the cycle, all sorts of vagaries may be noted At times, indeed, ovulation does not occur at all but the unruptured follicle undergoes degeneration without the formation of a corpus luteum Even so, an apparently normal menstrual period may appear at about the right time for the bleeding following withdrawal of the follicle hormone characteristically does not occur for a good many days Women with such a nonovulating or anovulatory cycle must, of necessity, be sterile, for they do not produce ova While this is relatively infrequent, it does explain a certain proportion of otherwise unexplainable instances of sterility The occurrence or nonoccurrence of ovulation in any cycle can be determined readily by securing for histological examination portions of uterine mucosa shortly before the expected date of menstruation

So far we have spoken only of the two ovarian hormones, but these are only links in the rather far flung endocrine mechanism of the reproductive cycle, involving as it does certain ductless glands in addition to the gonads One of the most fascinating stories in endocrinology is that embracing the discovery of the control of gonadal function by the anterior pituitary The credit for this belongs to two groups of investigators working independently and 3,000 miles apart, viz Smith and Engle in this country and Aschheim and Zondek in Germany Since the first publications of these authors in 1926 the nature of the pituitary control of ovarian function has been established fairly well It is exerted through two pituitary gonadotropic sex hormones, one producing maturation of the ovarian follicles, the follicle-stimulating hormone (FSH), and thereby motivation of estrogen, the other bringing about luteinization and thereby the production of progesterone the luteinizing hormone (LH) While there are still some who believe that these

dual effects may be manifestations of the differing effects of a single hormone substance the weight of evidence points to the actual duality of the pituitary sex hormones The dominance of the pituitary over the ovary is not an altogether one sided affair for their relationship is a reciprocal one When the production of ovarian sex hormones is excessive there is a reverse inhibition of the pituitary On the other hand when ovarian activity is at a low ebb or absent as after the menopause there is a relative increase in the production of pituitary gonadotropes

A third pair of hormone principles must be considered in any discussion of reproductive physiology The urine of pregnant women even in very early phases of gestation contains certain hormone principles which have long been spoken of as anterior pituitary like and which as a matter of fact were originally thought to be of pituitary origin However these principles were shown to differ from the pituitary gonadotropic hormones in certain crucial respects and as a matter of fact it has been clearly established that they are formed in the chorionic trophoblast They are therefore now properly spoken of as the chorionic or trophoblastic gonadotropic hormones Upon their presence in the urine of even early pregnancy are based the now universally employed biological tests for pregnancy such as the Aschheim Zondek and Friedman tests

While not directly related to the menstrual cycle mention of another gonadotropic principle seems necessary because it has achieved considerable therapeutic vogue I refer to the so-called equine gonadotropic principle obtained from the blood serum of the pregnant mare In animals it is dominantly follicle ripening in its effect and there is some reason to believe that it may have at least some effect on the human ovary However the evidence on this point is very conflicting as it is on the question of whether or not it may as some believe promote the occurrence of ovulation in non ovulating women In this respect the therapeutic use of this substance has run far ahead of its rationale

Even the male sex hormone principles are believed by some to play a part in the female reproductive cycle for it seems to be well established that the ovary like the testis is capable of producing both male and female sex principles As a matter of fact the androgenic substances especially testosterone propionate have attained considerable popularity in the treatment of certain menstrual disorders as will be discussed later in this chapter

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must take cognizance now of the important part played by the vascular apparatus and especially by the spiral arterioles of the endometrium. By the direct study of endometrium transplanted into the eye chamber of monkeys Markee has demonstrated the fundamental role of these coiled arterioles in the vascular phenomena of menstruation.

With reference to the hormone mechanism of menstrual bleeding the evidence of recent years has seemed to indicate that the responsible factor is a withdrawal or sharp drop in the estrogen blood level, thus knocking the props, as it were, from under the endometrium, which had been built up under hormonal stimulation. It was accepted rather generally that the catabolic phase thus induced in the endometrium is responsible for its desquamation, with the accompanying bleeding which we call menstruation.

There had always, however, been a minority of investigators who believed that the responsible factor is the withdrawal of the corpus luteum secretion, progesterone. The recent work on the chemical kinship of estrogen and progesterone makes this difference of viewpoint seem less sharp and less important than formerly, but it is of interest to note that authoritative investigators, especially Engle and Smith, have produced evidence to support the view that withdrawal of progesterone rather than of estrogen is the endocrine factor of prime importance in precipitating the actual bleeding of menstruation.

It would appear, however, that the broad concept of menstrual bleeding as a phenomenon due to endocrine withdrawal remains unchanged. Futhermore, the view that the ovarian hormone drop is induced by a reciprocal inhibiting effect upon anterior pituitary function still seems the most tenable, especially as Clauberg and Breipohl have shown that the inhibitory changes produced in the pituitary by progesterone and demonstrable by histological study, are quite similar to those produced by estrogen.

The Role of the Midbrain Areas in the Reproductive Cycle

In all discussions of the mechanism of menstruation it is upon the endocrine factors that much of the heaviest accent has been laid, first those originating from the ovary, more latterly also those arising in the anterior lobe of the pituitary. Indeed almost nothing is known of any other cogs in the menstrual machinery, though some must be of great importance. It is of interest, therefore, to note that physiologists are

now probing deeper than the anterior hypophysis in the elusive search for the deus ex machina of the reproductive cycle We must now encompass in our discussions of the subject at least a nebulous consideration of the probable roles of the posterior pituitary lobe the hypothalamus and the floor of the third ventricle already a sexual center located somewhere in the midbrain has been postulated

Perhaps the first intimations that the parahypophyseal portions of *the midbrain play a part in the reproductive cycle* emanated from the long discussion as to the seat of disturbance in certain abnormalities of the cycle and especially in the so called hypopituitary amenorrhea associated with the adiposogenital dystrophy of Frohlich This is not the place to review the fluctuations of the discussion throughout many years Suffice it to say that there now seems to be general acceptance of Smith s convincing demonstration that the metabolic disturbances of this syndrome are of hypothalamic and not of pituitary origin though the anterior hypophysis is responsible for the sex changes

The exact nature of the hypophyseo-cerebral relationship is not known and certainly there is no general acceptance of the view that the mingling of effects is due to an invasion of the hypothalamus by hypophyseal cells At any rate we can no longer hew too closely to the hypophyseal line in the consideration of the metabolic disturbances which so often are associated with amenorrhea There is some evidence too to indicate that an extrahypophyseal factor may be concerned in the frequent transitory weight increase of the normal human cycle Attention has been called to these by Sweeney as a result of weight studies of 42 normally menstruating women In 30 per cent of these he found an increase of 3 or more pounds during the period My own experience convinces me of the general correctness of Sweeney s observations (See also menstrual edema, Vol V Chapt XLIII-A and later on in this chapter)

There is considerable justification for the view that the cycle of menstruation involves not only the endocrine glands but also that certain areas of the brain are involved Evidence along this line is available in the studies of Hohlweg and Junkman upon the reverse effect of the follicle hormone upon the anterior lobe The work of Kunde d Amour Carlson and Gustavson that of Meyer Leonard Hisaw and Martin Moore and a host of other investigators has established the fact that continued injection of sufficiently large doses of estrogen brings about inhibition of the anterior pituitary sex hormone function This general conclusion is not invalidated by the study of Clauberg and Breipohl in

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associated as they are with certain hormonal body changes and yet so clearly involving nerve pathways And the examples might be multiplied

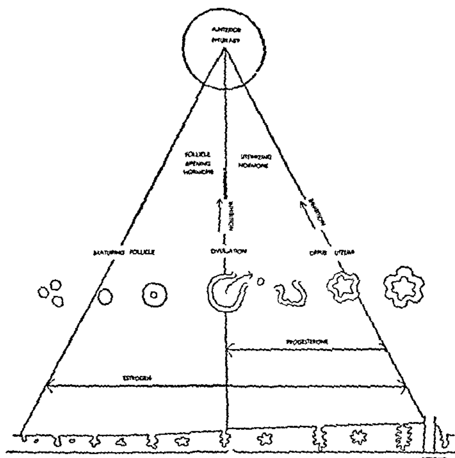


Fig. 1 This illustrates the roles of the two ovarian and two pituitary sex hormone principles in the cycle and also the reciprocal effect of the ovarian hormones upon the pituitary possibly by way of the "Sex Center" areas in the midbrain

THE CHEMISTRY OF THE SEX HORMONES

An outstanding development in the field of reproductive physiology during recent years has been the work on the chemistry of the sex hormones and especially the demonstration of the close kinship in the molecular structure of the male sex hormone the follicular hormone

which it appeared that a single large injection of estrin was followed by a sharp increase in anterior pituitary activity The latter conclusion, moreover, still needs confirmation

The special interest of the contribution of Hohlweg and Junkman lies in their conclusion that the inhibition of the anterior lobe is not a direct one upon the gland, but that it is mediated through a sex center in the midbrain If, for example, a second hypophysis is implanted into the kidney and the animal later castrated, only the normal hypophysis and not the implanted one shows the well known castration changes The conclusion therefore, is reached that the effect on the normal pituitary is not a direct blood borne one, but that it must be exerted through nervous channels affecting the normal gland but not the implanted one Hohlweg and Junkman, therefore conclude that there must be a sex center located in all probability in the floor of the third ventricle, as indeed had been suggested previously by Teel and Cushing as a result of the study of the effects of tumors in this region Schoeller suggests that this concept would explain the fact, first demonstrated by Philipp that the hypophysis of the pregnant woman contains so little of the gonadotropic principles in spite of their abundance in the urine While there seems to be good evidence for the existence in the parapituitary region of certain areas or centers vitally linked up with sex phenomena there is as yet no exact knowledge of the location of these centers or as to the nature of their link up with the endocrine organs

In all these studies there is manifest a strong new trend to seek beyond the endocrine glands for an explanation of the phenomena of the menstrual cycle as if there were not enough factors already to bedevil and confuse those trying to keep up with the march of developments As shown in Fig 1 we must now add another link to the diagrams which have become so popular in the representation of how menstruation is brought about

The chief significance of this extension of viewpoint would seem to be that it links up the endocrines and the nervous system That they are closely coordinated has always seemed certain on mere a priori grounds for those are parts of the body's system of intercommunication one primitive, the other highly developed Even psychic factors have been generally accepted as possible causes of menstrual disturbances and a beginning apparently has been made in exploring the pathways involved Again quite possibly we may have advanced a few steps toward an explanation of the vasomotor phenomena of the menopause

can determine only how much is eliminated Even this as Siebke emphasizes is inaccurate for such determinations deal with definite amounts obtained by one technic or another with no certainty that this reflects the amount of original hormone present in the blood and perhaps not indicated by the technic employed We do not know whether all of the variants of estrogen are essential for the female cycle or whether they represent only excretion derivatives This confuses blood and urine hormone studies a great deal, especially as there is the widest variation in the potency of the various forms of estrogen For example as Schoeller says if a (alpha) folliculin is excreted as the hydrate with a drop in potency from 8 to 10 million mouse units to 75,000 units per gram it can be seen that interpretations based on the urine hormone output necessarily would be very erroneous

As regards the chemistry of the corpus luteum hormone progesterone there has been the same intensive pursuit of its structural formula the pioneers being Allen Butenandt Slotta Ruschig and Fels Butenandt gives its chemical formula as $C_{21}H_{30}O$ and he with Westphal and Hohlweg in April of 1934 described the preparation of a crystalline chemically pure substance with this formula Here again there are a group of closely related substances to be dealt with

My purpose in discussing the chemistry of these hormones however is to emphasize first a fact which may be of great clinical importance viz the close structural relation which exists between the two ovarian hormones and between them and the male sex hormone androkinin or androsteron This is evident at once from the fact that all three of these hormones are built up around the same phenanthrene group composed of three six membered rings Phenanthrene itself rather curiously is quite inactive but the various sex hormone derivatives possess various types and degrees of physiological potency

Long before these fundamentally important facts had been established it seemed logical to believe that there must be some very close relationship between estrogen and progesterone for both are products of essentially the same cell Just as the lutein cell is only a modified granulosa cell so it seemed that progesterone would prove to be only a modified estrogen This indeed is what actually seems to be the case

Just as surprising as the relation between estrogen and progesterone is that which exists between the male and female sex hormones It has long been known that estrogen is at times found in the urine of men and the male hormone in the urine of women As a matter of fact perhaps the most surprising feature of Siebke s thorough study of the

and progesterone, as well as the remarkable relationship of all three of these to the well-known sterol group of chemical compounds, to the bile acids to certain vitamins and to various carcinogenic substances Moreover, a close chemical and physiological relationship has been established between progesterone and the desoxycorticosterone formed in the adrenal cortex When one considers that only a few years have elapsed since the discovery by Aschheim in 1927 that estrogen is present in large amounts in urine of pregnancy and that up to the opening up of this large source chemical studies of the hormone on any large scale had hardly been possible, one can appreciate the rapidity with which our knowledge has been advanced since then Within a few years estrogen in the form of estrone was obtained in crystalline form by Doisy and his coworkers, the crystals being for the first time exhibited by Doisy at the International Congress on Physiology held at Boston in August of 1929 At about the same time, and quite independently a similar accomplishment was achieved by Butenandt, *whose publication appeared a little before that of the American workers* Still other investigators reported similar results almost immediately afterward indicating what a hot trail all had been following

It soon became apparent that not all of these studies had yielded exactly the same substance but that estrogen existed in a variety of forms, so that soon it became necessary to distinguish between ketohydroxyestrin ($C_{18}H_{22}O_{2}$) or estrone and trihydroxyestrin ($C_{18}H_{24}O_3$) or estriol The former is the substance isolated by Doisy and also by Butenandt, while to Marrian is due the credit of *isolating the latter* Both occur in the urine of pregnancy, but ketohydroxyestrin is a far more potent physiological substance than is the trihydroxyestrin The estrogenic hormone is believed to be given off from the ovary in the form of dihydroxyestrin or estradiol There are marked differences in the degree of estrogenic activity of estrone estriol and estradiol All of these are clinically available in various commercial preparations

There are still other forms of estrone described (the alpha, beta and delta forms equilin hippulin etc), while almost nothing is known of its fate in the body except that *the liver plays an important part* in its destruction It has been suggested that the estrogen found in the urine of pregnancy is not identical with the estrogen produced by the ovaries There are many other unknown factors such as our uncertainty as to how much estrogen is produced in the body, how much is taken in with food how and in what chemical form it is utilized by the organs and how much of it is destroyed and where so that really we

can determine only how much is eliminated. Even this, as Siebke emphasizes, is inaccurate, for such determinations deal with definite amounts obtained by one technic or another with no certainty that this reflects the amount of original hormone present in the blood and perhaps not indicated by the technic employed. We do not know whether all of the variants of estrogen are essential for the female cycle or whether they represent only excretion derivatives. This confuses blood and urine hormone studies a great deal, especially as there is the widest variation in the potency of the various forms of estrogen. For example, as Schoeller says, if a (alpha) folliculin is excreted as the hydrate with a drop in potency from 8 to 10 million mouse units to 75,000 units per gram, it can be seen that interpretations based on the urine hormone output necessarily would be very erroneous.

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Just as surprising as the relation between estrogen and progesterone is that which exists between the male and female sex hormones. It has long been known that estrogen is at times found in the urine of men and the male hormone in the urine of women. As a matter of fact, perhaps the most surprising feature of Siebke's thorough study of the

hormone excretions of women during the menstrual cycle is the constant finding of the male hormone in the urine, though not in the feces From a quantitative standpoint the amount is not at all negligible a liter of urine containing an amount of the male hormone worth in Germany 10 R M at the then market value of the substance Indeed Siebke suggested female urine as a conveniently available source for the production of the hormone A more striking incongruity is seen in the case of horses for the urine of both the mare and the stallion is rich in estrogen

While the finding of the male hormone in women might be explained theoretically as due to the secretory activity of the potentially testicular elements normally present in the region of the rete ovarii in all women and while this explanation still is favored by some it is difficult to explain on corresponding histological grounds the presence of the female hormone in the urine of males It seems more likely that the reason is to be sought in the recently demonstrated closeness of chemical relation between the male and female principles Again we see in each the same phenanthrene nucleus, and the molecular formula of the male hormone differs from the female only by a molecule of water and an atom of carbon Zondek has suggested that in both sexes the male hormone is produced first being converted by dehydration into the female, probably under the influence of the metabolic processes which many consider to be of underlying importance in the matter of sex determination This explanation obviously would not apply to the paradoxical conditions existing in the equine family above alluded to

Thus it will be seen that this chemical relation of the male and female hormones is of fundamental importance as regards the question of sex specificity, sex differentiation and intersexuality More and more evidence is accruing to show that the cells of either type of gonad are capable of producing either male or female hormones As just one instance may be mentioned the cases of intersexuality which are characterized by dominantly female characteristics even though the only gonads present are testes This is illustrated in a case of my own and also in the case of similar nature also reported by Cadiz and Lipschutz in both of which typical menopausal symptoms followed removal of the patient s testes There is a considerable mass of evidence to the same effect available from the experimental laboratory

It requires no great stretch of imagination to conceive of the possible bearing of such observations upon the production of intersexual conditions particularly if one accepts the viewpoint championed by Witschi

and favored by many biologists that the cortex of the gonad is a determiner of femininity and the medulla a determiner of masculinity in the germ cells. In other words, a germ cell developing in the cortex will become an oocyte, that in the medulla a spermatocyte. This has been established clearly in such animals as the frog, and there is much to support it as regards the higher forms. If such facultativeness is exhibited by the dominating germ cells themselves, it would not be surprising if the character of the sex hormones also is susceptible of modification by environmental conditions.

The immediate advantage of securing the sex hormones in pure form is that it makes possible more precise study of their physiological roles. By contrast, the inability to prepare the various anterior pituitary hormones in pure form has been the greatest handicap in the study of their physiological action, not to speak of their therapeutic application. Again, it has been shown already that the potency of estrogen preparations is susceptible to enormous increase by means of chemical treatment, and now they can be prepared readily by synthesis.

Just what factor it is which in the mechanism of the reproductive processes determines the transformation of estrogen into progesterone, if such a transformation does occur, cannot be stated, though the obvious suggestion would be that it is dependent upon the interrelationships between the ovarian and pituitary functions, just as this interrelationship apparently determines the transformation of granulosa into lutein cells. Not only in the normal mechanism but also in certain pathological conditions is there seen such a transformation of granulosa into lutein morphology and function.

For example, in the well known granulosa cell group of ovarian tumors occasionally one may find a metamorphosis of granulosa cells into lutein-like cells (granulosa cell carcinome lipidique), and this change in morphology is reflected in the appearance of a decidual or predecidual picture in the endometrium. Such an endometrial response cannot, so far as we know, be brought about by any factor save progesterone, and there would seem to be no other source for the latter except the modified granulosa cells. In a case of this type reported by Novak and Brawner, the patient was ten years beyond the menopause, and there were, of course, no functioning corpora lutea in the ovaries.

There is still another angle of this new chemical work which has excited intense interest among investigators. I refer to the discovery of the close chemical relation which apparently exists between the sex hormones and the well known sterol group of chemicals, and particularly

the so-called carcinogenic substances, such as certain tar derivatives Here contact is made with the most important of medical problems that of cancer in general, and the rush of investigators to this new line of approach is ample evidence of the possibilities which it is believed to offer

With the sterol substances, including cholesterol, as with the bile acids, we have again to deal with the same three hexagonal rings of the phenanthrene nucleus which characterize the three gonadal hormones Curiously enough phenanthrene itself is inert so far as any biological effect upon the genital tract is concerned On the other hand, as Dodds and others have shown, certain sterols, when injected into castrated female animals, bring about definite estrous effects This rather startling observation would make us question the specificity of the hormones, to which alone such biological effects hitherto have been ascribed It would seem to throw light also on the occurrence of estrogenic principles in various bituminous minerals and in coal, peat, petroleum and crude oil The presence of biologically potent chemicals seems to offer a more probable explanation for this than does the view that these substances contain the locked up and still active female sex hormone existing in the plant life of millions of years ago That hormones play an important part in plant life apparently is now well established

Most provocative of all, however, is the fact that certain of the sterol substances are not only estrogenic but also carcinogenic There are a certain number of circumstantial observations, which even before this had suggested some sort of relation between the endocrine organs and cancer, such as the frequent positiveness of the Aschheim-Zondel test in cases of female genital cancer and the finding of large amounts of estrogen in the blood of cancer patients, even when these are males To these might be added the results of many experimental studies during the past few years such as those of Murray, Cook and Dodds, Overholser and Allen, Hofbauer, Geschickter, Lewis and Hartman and Lacassagne The last named for example, has reported the production of mammary cancer by means of the injection of oily solutions of estrogen into male mice of a strain in which this disease spontaneously affects only the female

To say, as some have done, that cancer is perhaps produced by derivation or deterioration products of the hormones, certainly is unjustified and premature but, on the other hand, the possibility that the closed door of cancer may be unlocked sooner or later by an endocrine key has been made more real by the chemical studies we have been discussing

On the other hand it is only fair to state that some investigators, notably Loeb are considerably less enthusiastic about the possibilities in this field In his review of the subject this author states that while carcinogenic hydrocarbons as well as regenerative processes or irritation may affect a great variety of tissues the estrogenic hormones are limited in their action to the tissues in which they induce growth processes during the normal sexual cycle' In any event, future years are sure to be exciting ones to those now pushing forward along this line of investigation The question of the possible hazard in inciting cancer through the therapeutic use of estrogens is discussed later in this chapter under the head of the menopause

Functional Gynecological Diseases

Amenorrhea and Hypomenorrhea

Functional amenorrhea and functional hypomenorrhea scanty menstruation may be discussed together because so far as is known the underlying causes are the same They constitute the largest and most important type of amenorrhea and hypomenorrhea for local causes other than the physiological ones are relatively uncommon and usually not difficult to recognize The causes of functional amenorrhea may be grouped into the constitutional and the endocrinopathic although it it not always easy to draw the line between them

Constitutional Amenorrhea and Hypomenorrhea—It has long been known that constitutional diseases of various sorts associated as they are with deterioration of the general health are often characterized by deficiency or absence of menstruation The latter therefore are frequent symptoms of tuberculosis chronic nephritis diabetes mellitus and similar dibilitating diseases Amenorrhea not infrequently is found in even incipient tuberculosis and it may indeed be the first symptom noted by the patient

The various forms of anemia are even more important in this regard None of the older textbooks failed to elaborate on the frequency and importance of chlorosis in this regard though now it appears to be a vanishing disease The explanation of amenorrhea produced by these debilitating diseases has in the past, been that it represents an effort on the part of nature to conserve the strength of the patient Nothing however, could be said of the mechanism The experimental studies of

McCollum and others, however, have demonstrated that the ovary is singularly sensitive to nutritional influences This is seen most clearly in the effects produced by deficiencies in the vitamin content of the diet, for dietary defects of this type quickly produce in animals a disappearance of the sex cycle That the same effect is produced in the human female was illustrated on a grand scale in the Kriegsamenorrhoe' so widely prevalent throughout the belligerent countries during the privation days of World War I The immediate ovarian effect produced by this cause probably is an interference with the maturation of the follicles and of course, with ovulation

The prevalence of self dieting, often extreme, among women makes this cause of amenorrhea of anything but academic interest While the diet of the average American woman contains a sufficient proportion of the essential vitamins, exceptions are at times found and are common in the case of women making strenuous efforts to reduce their weight

Little need be said as to the treatment of amenorrhea due to the causes enumerated here for it is obviously to be directed to the cause of the disorder For example, the rational procedure in cases of tuberculosis or anemia is the treatment of these conditions, in the management of amenorrhea due to dietary errors insistence on a properly balanced diet will effect a cure Perhaps the most important injunction is to abstain from any direct treatment of the menstrual disorder whether by the old fashioned emmenagogue drugs or by the more modern organ extracts Such measures are irrational, often harmful and almost always unsuccessful

Endocrinopathic Amenorrhea and Hypomenorrhea —This is perhaps the most frequent and most interesting of all types Its mechanism is varied and on this variation are based certain clinical syndromes presented by the patients placing them under different categories For example it is customary to speak of a *hypogonadal* and a *hypopituitary* type while *thyroid hyperfunction* and, less commonly *thyroid hypofunction*, likewise may be of causal importance It should be recognized however that these terms are not based on any exact knowledge of the nature of the relationship implied

In the so-called hypogonadal type the endocrine effect is believed to involve chiefly and perhaps only the ovary The prototype of this variety is the normal amenorrhea after the menopause or though not so physiological that seen after complete removal of ovarian tissue One would expect therefore to find the subjective and objective conditions similar to those seen after the menopause but there are numerous ex-

ceptions to this From a subjective standpoint it is true that vasomotor symptoms may be noted though they are rarely troublesome There may be moderate or at times marked adiposity with the heaviest deposits about the abdomen and hips In other cases however, where no other endocrine factor than the ovary can be demonstrated and where other constitutional factors likewise are lacking there may be no gain and perhaps even some loss of weight In short, the tendency has been to apply the designation of hypogonadal to cases in which these other factors cannot be established The precariousness of such a deduction is obvious

The endocrinopathic cause of amenorrhea for which the most satisfactory scientific evidence is available is that due to anterior pituitary deficiency This type of amenorrhea is associated with adiposity sometimes moderate at other times quite marked In one of my patients there had been a gain of 90 pounds (41 kg) in one year The deposit of adipose tissue shows a rather characteristic distribution often with large shoulder pads rather large bust a narrow waist and heavy deposits about the abdomen buttocks and hips *The hands are small and delicate* and the fingers slender and rather pointed There may be little in the way of subjective symptoms though headache pituitary headache sometimes is complained of This clinical picture has been established rather firmly *in the literature as adiposogenital dystrophy or Frohlich s* syndrome There has been much discussion as to whether all these symptoms are really of pituitary origin but the studies of Smith appear to leave no doubt that the adiposity is due to associated disturbance of *the adjoining hypothalamus while the changes in the genital tract are* unquestionably of anterior pituitary origin The fact remains however that there is often a clinical association between the two sets of changes so that the resulting syndrome still is designated commonly as adiposo genital dystrophy

Functional disturbance of the thyroid likewise may be characterized by amenorrhea or hypomenorrhea as one of the symptoms This is more frequently the case with hyperfunction than with hypofunction which in my experience is characterized more commonly by menstrual excess There are however numerous exceptions to both these statements thus confusing the exact nature of the thyroid influence on the menstruation As with amenorrhea of the hypopituitary type usually there is a tendency to obesity if the thyroid function is deficient The adipose tissue however is distributed more evenly with little tendency to the localizations described in connection with the pituitary variety and it may

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This statement does not, of course, apply to the far less frequent cases in which some organic lesion such as a pituitary tumor is present

Diagnosis —From what has been said it is evident that amenorrhea is merely a symptom of some underlying condition and not an entity in itself to be treated by this or that form of organic extract Every effort must be made to classify the individual case on the basis of careful history and physical examination with such aids as the laboratory can offer The latter often will mean such measures as blood and urine hormone tests, roentgenological study of the sella turcica urinalysis tests of sugar tolerance and studies of basal metabolism The more obvious types due to such definite diseases as tuberculosis and anemia are determinable by the usual diagnostic methods The history should be complete enough to bring out such factors as dietary defects changes in weight and endocrinopathic manifestations such as marked fluctuations of weight The physical examination will of course include such details important in endocrinopathic study as the presence or absence of obesity the distribution of the adipose tissue the distribution of hair the height of the patient and the condition of the pelvic organs

Treatment —There are a good many cases in which endocrinopathic amenorrhea needs no treatment others in which the treatment need be only a reassurance as to the essential harmlessness of the condition in itself and still others in which efforts at correction are definitely indicated To the first group belong the cases of moderate severity with no subjective symptoms in which pregnancy is not an important consideration For example a woman aged perhaps 35 to 37 whether married or unmarried usually will choose to forego any treatment if convinced of the harmlessness of the disorder and the usual unsatisfactoriness of the treatment She will be quite willing to resign herself to a premature menopause which is about what the condition represents

In women who have been much perturbed and depressed by the amenorrhea and especially when this upset is due to such erroneous ideas as I have mentioned previously the physician can perform a real service by explaining in simple language the real significance of menstruation stressing the fact that complete absence of the periods is compatible with good health In a considerable number however it is advisable to resort to treatment with a frank explanation to the patient as to its limitations

The third group presents the clearest indication for treatment It includes those cases in which there are definite associated symptoms and more particularly when an associated sterility, otherwise unex-

show some degree of the infiltrative myxedematous thickening seen so often with hypothyroidism.

If, as is more often the case, the amenorrhea is associated with hyperthyroidism, the well known characteristics of the latter condition are seen to greater or less degree. I need not stress the importance of studies of basal metabolism in the proper evaluation of these cases or in their proper management. For that matter, they can rarely be dispensed with in the proper interpretation of any endocrinopathic menstrual disorder.

Associated Symptomatology of Endocrinopathic Amenorrhea.—In a large proportion of cases there has been, in my experience, little or nothing in the way of subjective symptoms. At times, especially in the hypogonadal cases, there has been a complaint of vasomotor flushes, but only occasionally have these been very troublesome. The same thing may be said of the vertigo observed occasionally. Headache is not infrequent in cases of the adiposogenital dystrophy group.

Nervousness and depression are rather common, but I believe they are due in large measure to the psychic effect produced by the absence of menstruation. This, in turn, often is due to the wrong ideas held by many of the laity as to the significance of menstruation. The belief still is prevalent among the laity that the purpose of the menstrual flow is the purgation of the woman's system of impurities and that abolition of the function causes a retention of these harmful substances. Again a superstition often encountered, especially among the less intelligent, is that amenorrhea may lead to consumption, that the girl who does not menstruate is likely to "go into decline." This belief no doubt has its origin in the fact that in many cases of actual tuberculosis amenorrhea is an associated symptom.

In the case of married women who are anxious for pregnancy the sterility, which so often accompanies long standing amenorrhea, introduces another factor of the greatest importance in producing nervous and psychic symptoms. In general there is no doubt that amenorrhea greatly lessens the woman's chances for pregnancy, although exceptions are observed not infrequently. I have seen pregnancy supervene in a number of cases in which the women had not menstruated for several years. Taken as a whole, it is this group of cases of amenorrhea, i.e., those in which sterility is the underlying complaint, that most often calls for efforts at correction. Among women in whom the picture of the amenorrhea is not confused and overshadowed by the desire for children it is in a large proportion characterized by few or no symptoms, and the patient may be in as good health as if she had menstruated regularly.

ovulation I question therefore whether this combined plan has any advantage over the use of rather large doses of estrogen alone especially as the expense to the patient is very much greater

Treatment of Pituitary Cases—Much of what has been said concerning the treatment of the hypogonadal cases applies also to the management of those due to hypofunction of the anterior pituitary lobe The administration of thyroid and the enforcement of proper dietary restriction in the obese cases is important in both types Since ovarian function necessarily is impaired when there is marked gonadotropic deficiency estrogenic therapy often is of at least auxiliary value in the pituitary forms of amenorrhea Much more logical is the use of gonadotropic substances, for with these one might hope to start the ovarian mechanism and thus establish menstruation Unfortunately however the pituitary sex hormones as yet are not available, and the various gonadotropic preparations derived from the pituitary gland are impure and of very doubtful efficacy so that they cannot be recommended very enthusiastically

There is somewhat better ground for ascribing some efficacy to the gonadotropic preparations of pregnant mare serum which now are readily available These undoubtedly are effective in producing a follicle-ripening effect upon the ovaries of animals and there is some evidence that they have a similar effect on the human ovary At any rate such preparations represent about the nearest approach to gonadotropes as yet available for clinical use Some combine such treatment with the use of estrogens while others rely upon the pregnant mare serum preparations alone If the latter plan is followed the injections may be given subcutaneously or intravenously although the latter plan should not be employed without proper precautions against possible allergic reactions through preliminary dermal sensitization tests The subcutaneous plan is the safer for general employment

A better plan in my opinion is to combine the gonadotropic substance with the use of estrogens The latter may be given as recommended in the previous section for the hypogonadal cases but with each of the injections of the last three doses of estrogen there is combined a dose of the pregnant mare serum By this plan it is hoped that the endometrium can be more or less sensitized to the hoped for response from the follicle ripening principle of the pregnant mare serum

Other Measures in Treatment—In those cases associated with obesity the importance of proper caloric limitation of the diet is of great importance because there seems to be no doubt that reduction in weight

commercial preparations as hexestrol, dienestrol and meprane, to mention only a few

In general it appears undesirable in a chapter of this sort to mention any commercial preparations at all, especially as these are constantly being added to or subtracted from The same statement applies to proprietary oral preparations of the natural hormones, such as estinyl, benzestrol, premarin, etc and yet these few names are included simply to orient the reader in his plans for therapy Stilbestrol, which is cheap and effective, is a very potent estrogen, but it has the disadvantage that a certain proportion of patients, in my own experience from 10 to 15 per cent, cannot tolerate it because of such unpleasant toxic side effects as gastric unrest, nausea and vomiting or dizziness In such cases one of the other preparations of the same group, such as hexestrol dienestrol or meprane can be substituted, as all of these seem definitely less toxic Or one of the hormonal derivatives, such as premarin, estinyl or benzestrol may be resorted to

Taking stilbestrol as the example, 1 mgm may be given nightly for about 2 weeks, such nightly administration just before the patient retires being less likely to be followed by nausea and other unpleasant symptoms This is a fairly large dosage as a 1 mgm tablet of stilbestrol is looked upon by many as representing the estrogenic potency of 25 000 international units of estrone Bleeding does not take place during the administration of the drug but does a good many days, usually 5 to 10, after the last dose Such bleeding is due to retrogressive changes in an endometrium previously built up by the estrogen If bleeding does not take place within two weeks, the same course of treatment may be repeated As already indicated any other estrogen preparation including the natural hormones, may be used in appropriate dosage instead of stilbestrol

Combined Estrogen and Progesterone Therapy —The use of estrogens is combined by some with that of progesterone a favorite plan being to follow the estrogen as detailed in the preceding paragraph, with from four to six daily injections of a good progesterone preparation in a daily dosage of 10 mg intramuscularly or several times this by mouth This sequential administration of the two hormones is meant to mimic what happens in life and there is no doubt that even in castrate women the uterine histological cycle of menstruation can thus be substitutionally reproduced if sufficiently large doses are used However this does not alter the fact that any resulting bleeding is of artificial type that it does not stimulate the ovary, and that it does not produce

185 during the period of several months she was under observation but this drop in weight was punctuated by sharp rises of from seven to ten pounds occurring rather regularly at three-week intervals It was not uncommon for this patient almost overnight and with no intake of fluid or food to show this sharp rise of weight and this was accompanied by a lowered output of fluid and visible evidence of mild edema In other words she exhibited a three-week metabolic cycle even though there was no cycle of menstrual bleeding At the end of four months and possibly as a result of light hypophyseal radiation she began to menstruate her periods of bleeding coinciding with the weight increase

A search of the literature has shown the incompleteness of our knowledge concerning this interesting phenomenon of menstrual edema It presents some points of similarity and some of dissimilarity to the so-called Epstein nephrosis which however is not a cyclic phenomenon The first laboratory study of the subject appears to be that of Eufinger and his collaborators In Eufinger's first paper in 19 8 he found that 30 per cent of normally menstruating women exhibit a lessened stability of the blood colloids In another paper of the same year with Goldner it was shown by studies of the blood proteins that during menstruation there is a sharp rise in the level of globulin which may even be doubled while the albumin level drops correspondingly Usually by the end of menstruation the globulin content has dropped again to normal and the albumin has risen to its former level

In a third paper with Spiegler as collaborator (19 8) based on a study of twenty five normally menstruating women he presents evidence to indicate that this physiochemical disturbance of colloid structure is linked up with water metabolism leading to water retention during menstruation Incidentally as Eufinger and Spiegler show there has been much difference in the results of studies upon a possible chloride retention during menstruation In 47 per cent of the cases studied these authors demonstrated a water retention and tendency to edema during menstruation and at times during the immediately premenstrual period The more recent studies of Thorn Nelson and Thorn on the human and those of Krohn and Zuckerman on monkeys appear to have established definitely that the fluid retention is produced by the rising estrogen level in the latter part of the cycle

In these days of endocrine explanations it is hard to avoid thinking of the posterior lobe of the pituitary as in some way linked up with this phenomenon of cyclical water retention and of theorizing that this structure so overshadowed in gynecological interest by the anterior lobe

is in itself beneficial to a restoration of normal endocrine equilibrium and normal ovarian function I have observed a good many obese, amenorrheic patients in whom simple dietary reduction of weight was followed by re-establishment of menstruation, so that further organotherapy of the amenorrhea, which had been contemplated, was rendered unnecessary Had ovarian therapy been instituted synchronously with the reduction in diet, it might have been given undeserved credit for the correction of the amenorrhea

The treatment of this form of amenorrhea by means of light dosage of x-rays has been much discussed in recent years and a number of articles have been published showing apparently good results The entirely empirical nature of such treatment, the impossibility of limiting the action of the rays to certain cells without affecting others also, and the still existing uncertainty as to harmful results and the possibility of injurious effects upon later offspring as a result of this treatment have always deterred conservative gynecologists from any very frequent resort to this plan Moreover, it is most frequently unsuccessful in the re establishment of the menstrual function and it is significant that a number of authors who previously had expressed great enthusiasm for the method now use it only rarely

Menstrual Edema

There has been much interest in a group of cases described by Thomas in 1933, in which the menstrual weight increase was exaggerated and obviously was due to a generalized edema I have seen a considerable number of such cases over the years In one of these the gain of weight was as much as fifteen pounds, and the edema during the menstrual period was very obvious with swelling of the face tissues, puffiness of the eyelids and swelling and pitting of the feet and ankles In two of the patients, in whom there was an opportunity for daily complete study it was easy to demonstrate marked fluid retention during menstruation with polyuria and rapid disappearance of the edema after the period

Of special interest was a patient of twenty-one, who suffered with complete amenorrhea of three years' duration, together with enormous adiposity her weight being 232 pounds She responded quite favorably so far as weight was concerned to a low caloric diet together with the administration of moderate doses of thyroid, even though her basal metabolism rate was very little below normal Her weight dropped to

In the milder forms there may be only extreme nervousness and rest lessness but in the severe types the condition of the patient may border on the psychopathic with striking change of personality and emotional outbursts which make her very difficult to manage Loss of inhibitions may be manifested as well as imperative ideas In one of my cases the patient had an uncontrollable desire to throw her children to whom she was devoted out of the window

From what has been said as to the mechanism of the disorder it can be seen that it appears closely related to premenstrual edema and the two not infrequently coexist Ulcerative stomatitis has been noted in some of the cases I have in a few patients who had received very large and prolonged dosages of estrogen noted a condition of nervous tension not unlike the premenstrual type this supporting the general belief that estrogen excess is the responsible factor

The *treatment* of the condition is like that of menstrual edema not by any means a standardized one When the condition is seen in women approaching middle life and the symptoms are of severe type the induc tion of the menopause generally is advisable and always is effective if sufficient radiotherapeutic dosage is given In milder cases and in the younger group of patients the various methods of treatment mentioned in the preceding section menstrual edema have all been tried

A promising relatively new plan has been suggested by Greenhill and Freed who believe that the ovarian steroids are responsible for sodium *ion retention by the body tissues and that the neurological symptoms* are due to the resulting edema of the nervous system especially the brain On this hypothesis they advocate the oral use of ammonium chloride and by this medication they feel that excess sodium and fluid can be withdrawn They report uniformly good results in 15 patients in whom the method was used The dosage of ammonium chloride advised was gr x (0 6 gm) three times daily during the last two weeks of the menstrual cycle During this time the patients were instructed to refrain from the use of table salt and to avoid taking sodium bicarbonate

Primary or Essential Dysmenorrhea

This affection commonly is relegated to the category of 'minor gynecological disorders but it is one of the everyday problems in the work of the general practitioner as well as the specialist The patients themselves would scarcely acquiesce in its designation as a minor dis-

may participate in the cyclical changes of menstruation, and that in some way its admittedly antidiuretic function is increased during menstruation. The problem is, of course, not so simple as all this as one will soon learn if one begins to look into the intracacies of the water balance. A very superficial peep was enough to discourage me from attempting any discussion of this problem.

My reason for including this subject in this chapter is simply to stress the fact that in the endocrinopathic weight increases, so frequently observed in gynecological practice, one must take cognizance not only of a metabolic disturbance characterized by actual deposit of fat but also of the factor of water and possibly chloride retention, manifested in some degree even in many normally menstruating women and to a more striking degree in the occasional cases of generalized menstrual edema. It is quite certain that these two types of disturbance may coexist in the same patient. See also Vol V, Chapt XLIII-A for additional discussion.

In the mild forms of menstrual edema associated with weight gains of only a few pounds and with perhaps only a slight feeling of puffiness or bloating no treatment is necessary. In the more exaggerated types efforts at relief are indicated. The experience of Atkinson and Ivy who reported good results only from the placental hormone emmenin does not seem to have been duplicated by other observers. Mazer and Israel advocate the use of progesterone in doses of [illegible] units every other day beginning at about the time of ovulation and continuing to the next period. Testosterone propionate has been used by others including myself, *in a dose of gr 1/6 (10 mgm) two or three times a week.* More recently Greenhill and Freed have reported excellent results from the administration of ammonium chloride in a dose of 10 grains (0.6 gm) three times a day as in the treatment of premenstrual tension described in the next section.

Premenstrual Tension

While relatively rare this condition may be a very distressing one. The earliest studies on this problem were made by Frank who related the symptoms to estrogen retention produced by a high renal threshold of excretion. The direct cause of the symptoms would seem to be a disturbance of the automatic nervous mechanism. Mazer and Israel on the other hand explain the estrogen retention as due to inadequate utilization of the hormone "by reason of a deficiency or total absence of the corpus luteum hormone progestin."

enough by the proper examination. It may be a severe anemia, tuberculosis, diabetes or any one of many other systemic disorders. In the strict sense, therefore, the dysmenorrhea in such patients is secondary rather than primary, although the pelvic organs themselves are normal. Certain it is that many such patients can be relieved of the dysmenorrhea by correction of the underlying cause, with the institution of the proper hygiene, exercise and other indicated measures.

Even more important, although much more difficult to evaluate, is the psychogenic factor, which undoubtedly is concerned in many cases of primary dysmenorrhea as with other functional disorders. Indeed *there are some gynecologists who believe that all cases are of psychogenic origin,* a generalization to which I cannot subscribe. Such authors lay much stress upon Freudian factors, but explain other cases as due to such causes as mental shocks at or near the menstrual period, with the subsequent development of a conditioned reflex mechanism, suggestibility, as when a girl has been reared in the same household with a dysmenorrheic mother, a feeling of revulsion at the offensiveness of the menstrual discharge, *and so on.*

I am convinced personally that the psychogenic factor is the important one in a considerable number of cases, but I feel just as strongly *that it cannot explain all. Every gynecologist must encounter patients* in whom no such factor can be brought out, who perhaps are of a very phlegmatic temperament and who apparently possess normal bodies and minds. Psychiatrists with whom I have *talked tell me that the assumption* of a universal psychogenic factor in the explanation of primary dysmenorrhea would be far fetched.

Still another factor remains to be considered, that of the possible role of certain endocrinopathies. Dysmenorrhea may at times be encountered in patients with well defined endocrine disorders, but most often it is not. There have, of course, been many speculative attempts to explain this affection on an endocrine basis, but until recently nothing of a scientific nature had been contributed. Investigations upon the question of the hormonal regulation of uterine contractility have yielded results which seem applicable to the clinical problem of dysmenorrhea. The very nature of the pain in these cases would, of course, suggest an origin in an exaggerated or disordered contractility of the uterine musculature. The investigations of Knaus, Reynolds and a number of others throw much light upon this problem. They are discussed fully in the paper of Novak and Reynolds, based on the latter's studies on the vari-

order, for it is, in the aggregate, the cause of more suffering and invalidism than many conditions dignified by the appellation "major"

While the earlier literature is full or articles upon primary dysmenorrhea almost nothing of solid nature can be crystallized out from them for they are almost altogether of a speculative nature both as to the etiology and the therapeutic measures recommended Only within the past few years with the intensive study of the female reproductive system has there appeared a hope of solving the problem of the mechanism and the treatment of this extremely common ailment

With the secondary type of dysmmenorrhea associated as it is with some definitely recognizable pelvic abnormality an explanation of the menstrual pain usually is evident and the indication for treatment clear With the primary variety and it is with this alone that we are concerned here the pelvic organs are characteristically normal although the patient may suffer excruciating menstrual pain Most often although not invariably this begins 1 or 2 days before the actual menstrual onset and ceases after menstrual bleeding is well established usually after the first day As is well known, the affection is seen most often in young unmarried women or in married nullipara

The time honored view was that the dysmenorrhea is the results of an obstruction to the exit of menstrual blood most often because of a kink associated with anteflexion There are many reasons why this cannot explain most cases not the least being the frequent observation of severe dysmenorrhea without anteflexion or obstruction of any kind and vice versa, of very sharp anteflexion *with no pain whatsoever*

Equally unsatisfactory is the evidence for the importance of hypoplasia of the uterus as a cause of primary dysmenorrhea For example a large proportion of dysmenorrheic patients date the onset of the menstrual pain not from puberty but from a period several or perhaps many years later This observation is hard to check up with the essential causal importance of a primary hypoplasia of the organs present from birth Furthermore the uterus of the dysmenorrheic patient often is quite normal in size

Not so easily dismissed however are two other factors the constitutional and the psychogenic The first of these unquestionably will explain a certain proportion of cases just as it will explain the production or exaggeration of other subjective symptoms Apparently here we have to deal with a lowering of the threshold of pain so that the normally slight menstrual discomfort is magnified into an actual dysmenorrhea Most often the constitutional depravity is obvious or is revealed readily

enough by the proper examination It may be a severe anemia tuberculosis diabetes or any one of many other systemic disorders In the strict sense therefore the dysmenorrhea in such patients is secondary rather than primary although the pelvic organs themselves are normal Certain it is that many such patients can be relieved of the dysmenorrhea by correction of the underlying cause with the institution of the proper hygiene exercise and other indicated measures

Even more important although much more difficult to evaluate is the psychogenic factor which undoubtedly is concerned in many cases of primary dysmenorrhea as with other functional disorders Indeed there are some gynecologists who believe that all cases are of psychogenic origin a generalization to which I cannot subscribe Such authors lay much stress upon Freudian factors but explain other cases as due to such causes as mental shocks at or near the menstrual period with the subsequent development of a conditioned reflex mechanism suggestibility as when a girl has been reared in the same household with a dysmenorrheic mother a feeling of revulsion at the offensiveness of the menstrual discharge and so on

I am convinced personally that the psychogenic factor is the important one in a considerable number of cases but I feel just as strongly that it cannot explain all Every gynecologist must encounter patients in whom no such factor can be brought out who perhaps are of a very phlegmatic temperament and who apparently possess normal bodies and minds Psychiatrists with whom I have talked tell me that the assumption of a universal psychogenic factor in the explanation of primary dysmenorrhea would be far fetched

Still another factor remains to be considered that of the possible role of certain endocrinopathies Dysmenorrhea may at times be encountered in patients with well defined endocrine disorders but most often it is not There have of course been many speculative attempts to explain this affection on an endocrine basis but until recently nothing of a scientific nature had been contributed Investigations upon the question of the hormonal regulation of uterine contractility have yielded results which seem applicable to the clinical problem of dysmenorrhea The very nature of the pain in these cases would of course suggest an origin in an exaggerated or disordered contractility of the uterine musculature The investigations of Knaus Reynolds and a number of others throw much light upon this problem They are discussed fully in the paper of Novak and Reynolds based on the latter s studies on the varia

tions in uterine contractility under various conditions and under the influence of certain hormone factors

To summarize these only very sketchily, Reynolds found, by an ingenious method of study, that (1) uterine muscle exhibits a normal rhythm of contraction, (2) all uterine contractions disappear after castration, (3) they are restored by the injection of estrogen (4) the *contractions produced by estrogen are inhibited by the injection* of progesterone or of the urine of pregnant women, (5) the normal excitant of uterine contractility is the follicle hormone, while the corpus luteum principle, progesterone, is an inhibitor

On the other hand, the work of other investigators, like Wilson and Kurzrok, has thrown doubt upon the supposed inhibitory effect of progesterone on uterine contractility, and as a matter of fact, we cannot even be sure that a heightened muscular contractility is the immediate factor in the production of the pain, although the character of the latter suggests the correctness of this view Again, dysmenorrhea *is* characteristically absent in women with anovulatory cycles, in whom estrogen alone is present with no progesterone To put it another way the mere fact that a girl has a typical primary dysmenorrhea is reasonably good evidence that she ovulates with her menstrual cycles as the work of Sturgis and Albright has shown These facts are difficult to reconcile with the view that progesterone inhibits uterine contractility, and it is possible that other unknown factors may be involved also Finally the results of progesterone therapy in primary dysmenorrhea have been notoriously disappointing as will be discussed later, so that the whole question of the mechanism of this type of menstrual pain still must be considered an open one

Treatment —The management of cases of primary dysmenorrhea obviously must be directed toward two objectives (1) the treatment of the attacks themselves and (2) the permanent relief of the condition These will be discussed in at least a brief and summarizing fashion

The Dysmenorrhea Attack Itself —When confronted with a patient suffering the often excruciating pains of primary dysmenorrhea, the physician s immediate concern is with the relief of pain The *first injunc*tion to be borne in mind, perhaps is to refrain from the administration of morphin for not a few women addicts date their affliction from the use of morphin for this condition Alcohol should be prescribed with equal caution While of undoubted benefit in the form of either whiskey or of some of the alcohol laden proprietaries there is danger in its use Cases of moderate severity often are relieved by the simpler analgesics

such as codein or acetylsalicylic acid together with rest in bed hot applications and hot drinks

From what has been said as to the causative role of exaggerated and painful muscle contraction the administration of antispasmodic drugs would seem to be called for One of the best of these in my experience is atropin sulfate as I discussed in a paper published many years ago This is administered by mouth in doses sufficient to cause mild saturation symptoms An average dosage is 1/120 gr (½ mgm) every 4 hours beginning from a day to several days before the period depending on the usual time of onset of pain In a considerable proportion of cases great relief is obtained

However such physiological considerations as I have discussed in this chapter suggest that more rational and perhaps more effective antispasmodics may now be available The biological inhibitors of uterine contractility on the basis of laboratory investigations are progesterone testosterone and the luteinizing principle of the urine of pregnant women All are available now for clinical use, and the short experience we have thus far had with them is encouraging

Endocrine Therapy—The several endocrine approaches to the therapy of dysmenorrhea may be summarized briefly as follows

1 The pregnancy urine preparations or progesterone may be given beginning usually a week or so before the usual onset of the pain in injections given ordinarily every other day or so and kept up until menstruation is established after which dysmenorrhea of this type ordinarily does not continue anyhow If the pregnancy urine preparations are used the dosage varies from 200 to 500 units if progesterone is employed, the doses vary from 1 to 5 mgm 5 rabbit units depending not infrequently on the patient's pocketbook for the larger doses entail considerable expense While good results have been reported by some especially with progesterone most often both the patient and the doctor will be disappointed

2 The use of testosterone is predicated not only on its inhibiting effect upon the musculature but also upon its effects upon the ovarian hormones Though there is still some confusion on this point it would seem from available studies that probably through the medium of the pituitary testosterone in the early stages of the cycle lessens the production of the estrogenic hormone In the later stages curiously enough it seems to accentuate the effects of progesterone For these reasons the rational plan would seem to be to keep up the administration of testosterone usually in the form of the propionate throughout the cycle

There is still no unanimity of opinion as to the dosage to be used my own preference being for smaller doses than many have employed as they appear to accomplish about as much as the larger amounts without certain disadvantages of the latter which will be discussed presently Ten milligram doses given twice or three times a week often will suffice and larger doses than 25 mgm twice a week are not employed in my own work Others have employed doses totaling several hundreds of milligrams monthly

The results with testosterone propionate therapy have been gratifying much more so than with the plans previously mentioned On the other hand, every one has had to take note of certain unpleasant risks which accompany this use of testosterone in women A small number of cases have been reported, in which testosterone therapy has been followed by hirsutism and in one or two instances by deepening of the voice and slight hypertrophy of the clitoris There is every reason to believe that such changes are transitory, and this indeed is indicated in the data of most of the published cases Moreover, the dosage in the reported cases has been considerably larger than many of us employ

While I have not, in the considerable group of cases in which testosterone has been employed seen any evidence of masculinization changes the fact remains that, if such unpleasant sequalæ prove to be at all common, most of us would be very hesitant in the use of this hormone, even though the undesirable symptoms always were transient My own attitude as present is to continue this method where it seems to be indicated because of its frequent efficacy but always in the smaller doses which I have mentioned, and with a watchful eye for unpleasant side effects

3 Finally, attention may be called to the employment of the estrogenic hormone in the treatment of dysmenorrhea The plan which has been employed by certain authors of administering estrogens premenstrually, always has seemed to me unsound On the other hand, the use of estrogens in the first half of the cycle with the idea of promoting uterine development is much more rational and has been employed by me for many years especially when the uterus is hypoplastic

However an entirely new indication for estrogenic therapy in dysmenorrhea has been evolved very recently from the studies of Sturgis and Albright It now seems possible to convert an ovulating cycle into an anovulatory one by administering estrogens in adequate dosage in the early part of the cycle and often such inhibition of ovulation brings about relief from pain with the next flow The suggested plan found

effective in every one of 25 cases of primary dysmenorrhea, is the intramuscular injection of 10 000 international units of estrogenic hormone every third day for from six to ten injections beginning no later than the sixth day of the cycle The surprising thing is that ovulation could be prevented so precisely and uniformly in every one of the cases studied by the above authors In a considerable number of cases in which I have employed this method the relief from pain has been quite complete

Unfortunatey the benefits from this treatment as well as from treatment with testosterone do not extend beyond the next succeeding period Even this temporary relief is a boon to the patient who has come to dread the advent of menstruation because of the severe suffering it entails and those, in whom the dysmenorrhea is very severe no doubt would prefer to have a short series of injections repeated from time to time rather than suffer the menstrual pain Aside from this the psychic lift given by this treatment in getting the patient out of a pain groove and the beneficial effects of the estrogenic substance, when this is used in promoting uterine development are not unimportant considerations It seems likely that after treatment has been kept up for a number of months some of the patients might be able to dispense with it though our experience with this plan is too recent to speak on this point It offers a new approach in the endocrine treatment of this troublesome disorder and would seem to call for further trial and study

Measures Looking to Permanent Relief—The time honored view that primary dysmenorrhea is cured by the first pregnancy is in the main, correct although many exceptions are encountered Marriage however cannot be prescribed as complacently as medicine

The factor of hypoplasia considered so important by some gynecologists and undoubtedly present in some cases can, I believe, be helped by the use of estrogen Indeed I know of no other intelligent method of accomplishing this The administration of estrogen to animals brings about marked overgrowth of the uterus with hyperemia With full allowance for the uncertainties and the probable inadequacy of dosage for the human the use of estrogen is indicated in primary dysmenorrhea associated with underdevelopment of the uterus The administration of 0 5 mg daily doses of stilbestrol for 6 days, beginning just after menstruation is the usual plan I have followed In other words, all the estrogen is given during the follicular phase of the cycle

The resort to cervical dilatation so common in the past and even at the present day, is of course based on the older idea of the obstructive etiology of dysmenorrhea now rather generally abandoned That it

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interested in outdoor sports and engendering in her mind a pride in her physical development

Finally in the occasional extreme case in which an intelligent use of the various measures, which have been discussed yields no improvement the operation of presacral sympathectomy may be resorted to with good results in a large proportion of cases

Results of Treatment —The fact remains that a plan of treatment based upon the constitutional psychogenic and endocrine considerations which have been discussed will rarely fail to benefit the patient and at least to make her lot a very tolerable one Those who approach the problem along these broad gauged lines will not find frequent need for more radical procedures such as *sympathectomy* or even *hysterectomy* It may be stated as almost an axiom that the gynecologist who reports large numbers of sympathectomies has failed to take full advantage of the less radical plans of treatment which so often will bring about cure or at least marked amelioration of menstrual pain

On the other hand the operation of *presacral neurectomy* or *sympathectomy* is a rational and frequently effective procedure in the occasional case of unusually severe dysmenorrhea which has been intractable to more conservative procedures It gives complete or almost complete relief from pain in probably 60 to 70 per cent of cases While it may be indicated in primary dysmenorrhea per se an even more frequent application at least in my hands has been as a supplementary procedure in conservative operations done for such conditions as endometriosis or marked retroflexion when these are associated with severe dysmenorrhea The surgeon may not be at all sure that a conservative operation done for such indications will give satisfactory relief from menstrual pain and under such circumstances since the abdomen has already been opened the supplementary performance of a neurectomy is more likely to ensure a good result

Nothing much need be said as to the treatment of the *dysmenorrhea attack* itself for nothing new can be added The local use of heat and analgesics of one sort such as codeine and acetylsalicylic acid will suffice for all except the occasional case Too much stress cannot be laid on the risks of resorting to the two drugs which will always relieve the pain morphin and alcohol That the danger of drug addiction is not a fanciful one I have had the opportunity of observing in a number of unfortunate instances

Summary of Management —Any explanation of such a subjective pain disorder as primary dysmenorrhea which is based purely on endo-

has been effective in at least a fraction of the cases permits of no doubt but the doubt arises in trying to determine the mechanism of its effect Is it entirely psychic, or is it based upon a real virtue in the dilatation One cannot be dogmatic, but there can be little question that in many cases the operation is a form of psychotherapy, at times successful although not infrequently only temporarily This is not a radical statement for it can be made of many other measures, which have been used for this condition and as a matter of fact there is no doubt that many cases of the psychogenic variety are cured without either drugs or surgery

With reference to this last group the physician should never forget that the psychic factor must always be borne in mind so that a careful history should be obtained, especially as to the time of onset of the dysmenorrhea with a possible correlation of this event with a psychic trauma of one sort or another As already stated I do not believe that such an etiology can be demonstrated with the constancy claimed by some authors but not infrequently it can Furthermore whatever the cause of the first attack may be, there is always the possibility that the factor of fear may lead to recurrence and perpetuation of the symptom The subject is as involved as are many other psychiatric problems but a good history interpreted along broad and sane lines usually will lead to a proper evaluation of the individual case

Every such gynecological consultation should be an educational one from the standpoint of the patient the physician taking the time to reassure her as to the significance and normality of the menstrual function of the fact that it is commonly associated with very little discomfort and that it should cause little or no interference with her usual activities and so on In many instances the mothers of dysmenorrheic young girls are in greater need of such education than the patients themselves for too often the girl at puberty is coddled into the belief that the menstrual period is a time of semi invalidism and physical discomfort requiring abstention from exercise of all sorts and almost a species of segregation This picture is not overdrawn, although in recent years a far healthier attitude gradually is coming to prevail

Only an additional word need be added as to the importance of general constitutional building-up and measures of general hygiene This topic need not be elaborated although it is an important one Repeatedly I have seen dysmenorrhea disappear entirely with no direct treatment of the pelvic disorder itself by encouraging the patient to get

interested in outdoor sports and engendering in her mind a pride in her physical development

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crine considerations, and which does not take cognizance of constitutional and psychogenic factors as well, is inadequate as a basis for the management of these patients While endocrine factors alone may be responsible in some cases, the same is true of constitutional or psychogenic factors, and in most cases more than one of these three chief etiological factors coexist

As a part of the treatment of primary dysmenorrhea endocrine therapy may properly be employed, but the physician, who depends upon it entirely, and who takes no recognition of other possible factors is sure to meet with failure in a large proportion of cases

I confess that the longer I practice, the less enthusiastic I am about the endocrine therapy of dysmenorrhea, and I try to get along without it if possible For example, in a large proportion of dysmenorrhea patients the severe pain is limited to perhaps one day and sometimes only a few hours In such cases it seems to me unwise to start a girl off on a career of organotherapy A few fairly generous doses of codein and aspirin usually will tide the girl over the worst of her trouble In addition to this general and constitutional measures psychotherapy and reassurance, with advice to try to remain up and about rather than going to bed during the pain attack seem preferable to the uncertainties and inconvenience of endocrine therapy When the dysmenorrhea is more protracted and severe however, endocrine therapy should be added before resorting to more radical measures such as presacral neurectomy

The evidence now clearly indicates what had long been suspected, *that primary dysmenorrhea is a disorder of ovulating women*, and that it is probably relievable by preventing ovulation This apparently can be done for the particular cycle at least by rather large doses of estrogenic substance started very early in the cycle The method is too new to permit of clinical evaluation, but it would seem that it should be of value in the management of some cases Other hormone preparations which frequently will be helpful are testosterone propionate progesterone and the chorionic principle of pregnancy urine

Functional Uterine Bleeding

This very common and often very distressing functional disorder is seen characteristically in women at or near the menopausal age on one hand or during the pubertal or early adolescent years on the other though it is not infrequent at any age during the reproductive epoch

The bleeding in these cases may be very severe or even exsanguinating even though the pelvic organs be grossly normal

In so far as the ovarian hormones are concerned the mechanism of this disturbance seems now to have been established clearly The important defect appears to be a failure of ovulation so that the follicle continues to develop beyond the normal ovulation period and what is most important to produce a steadily increasing amount of estrogen So long as the endometrium is being thus supplied it continues to grow and bleeding does not occur Clinically we know that such patients often exhibit non bleeding phases of even many weeks so that with the final onset of free bleeding there is not infrequently and not unnaturally a suspicion of early abortion The endometrium subjected to such persistent and excessive estrogen influence undergoes a slow vegetative proliferation assuming often the picture designated as hyperplasia

As has just been said so long as the endometrium is receiving a steady supply of estrogen bleeding does not occur How then can we explain the bleeding phases sometimes short more often prolonged often periodic not infrequently very irregular not rarely continuous? On the basis of what is now accepted as to the hormone mechanism of menstrual bleeding in the human female or of estrous bleeding in some of the lower animals the obvious explanation would be that the estrogen blood level undergoes drops at varying intervals and that it is this estrogen withdrawal from the endometrium which is responsible for the bleeding

What explanation however can we make as to these intermittent drops in the estrogen level? For this we must turn to the reciprocal relations existing between the ovarian and anterior hypophyseal sex hormones While it is true that the anterior pituitary lobe is the motor of the ovary and that failure of anterior pituitary function means a failure of ovarian function it has been established that the ovary in turn exerts a reciprocal effect upon the anterior lobe The work of Moore Hisaw and his collaborators as well as other investigators has shown that prolonged and excessive estrogen administration is followed by inhibition of the anterior lobe function and that with the latter in abeyance there follows an inhibition of ovarian activity

In our cases of functional bleeding a similar mechanism seems to operate so that when the estrogen level reaches a certain point there is produced an inhibition of the anterior pituitary and in turn an inhibition of follicular activity in the ovary with the drop in estrogen which is responsible for the bleeding phase I have compared the mechanism to

that employed in our automatic heating systems, in which the production of heat is shut off automatically when the temperature of the house reaches a certain level The interlocking relationship between the two glands thus is seen to be not only qualitative but also quantitative, and this is true of endocrine relationships in general, a fact often overlooked

While the above mechanism would seem to apply to the largest proportion of cases, it has been established that not all cases of functional bleeding can be fitted into one mould For example, in some cases there is no failure of ovulation, and the explanation must be sought in othe factors such as a quantitative imbalance between estrogen and progesterone, deficiency of the uterine musculature or disturbances referable to the spiral arterioles of the endometrium For a fuller discussion of these factors the reader must be referred to textbooks on Gynecology or Female Endocrinology

Treatment—The treatment of this disorder is influenced by two chief factors, the age of the patient and the importance or unimportance of preserving the reproductive function

First of all it should be remembered that no sharp dividing line can be drawn between the quantitatively normal menstrual periods not infrequently associated with the anovulatory mechanism, and the pathologically excessive bleeding, in which the same underlying mechanism is concerned Just as the girl at puberty often exhibits anovulatory cycles, which by spontaneous readjustment of the hormone mechanism become ovulatory in character so may similar spontaneous readjustment of the *mechanism bring about spontaneous cure of functional bleeding* This is particularly true of the milder forms of bleeding so often seen in the pubertal and premenopausal periods of life A considerable proportion of girls exhibit not only marked irregularity but also moderate excess of menstruation for periods of from several months to several years after initiation of the function And many of these then without treatment fall into a normal menstrual swing A similar observation may be made in women approaching the menopause a certain proportion of whom unquestionably cease ovulating a considerable time before they cease menstruating Such anovulatory cycles may be moderately excessive While we very properly teach women that flooding at this time is never to be looked upon as normal the fact remains that many women who disregard this teaching cease bleeding spontaneously through final cessation of ovarian function

Treatment in Menopausal Group—When however, the abnormal bleeding becomes very free or alarming the patient is quite sure to seel

advice If she is in the menopausal group the treatment is simple and highly satisfactory At this age the first essential is to make sure that the bleeding is really functional and that no structural lesion such as uterine or ovarian neoplasm is present If pelvic examination reveals no evidence of this the next step is to eliminate intrauterine pathology and especially adenocarcinoma of the uterus This can be done only by *diagnostic curettage and microscopic examination* If the latter reveals an endometrium of proliferative or hyperplastic type or even one corresponding to any of the normal menstrual phases it is fair to conclude that the bleeding is of functional origin

Once this has been settled the further management is clear Women at this phase rarely are anxious for further pregnancies and practically 100 per cent of such cases can be cured by abolishing ovarian function by radiotherapy This is not the place to discuss the technique of the latter procedure but an effort should be made to give sufficient dosage to abolish ovarian function completely Some ovaries are notoriously hard to kill and after insufficient dosage bleeding may reassert itself in from a few months to several years This may be disconcerting because while such bleeding is very likely to be again of functional nature it is difficult without repetition of diagnostic curettage to eliminate an intercurrent intrauterine carcinoma All in all however the treatment of functional menopausal bleeding represents one of the most satisfactory applications of radiotherapy in the field of gynecology There is rarely any justification for hysterectomy unless there is some other indication for opening the abdomen in which case there can be no objection to simple removal of the uterus

Treatment in Younger Patients—The problem is far more difficult and unsatisfactory in younger patients in whom the matter of future reproductiveness usually is of the greatest importance not to speak of the importance of preserving ovarian endocrine function In the case of very young patients curettage usually is not necessary for diagnostic purposes and if simple pelvic examination reveals the essential normality of the pelvic organs there is little risk in assuming that the bleeding is of functional nature Occasionally curettage is necessary for its immediate therapeutic effect for it rarely fails to check the bleeding temporarily It need hardly be added that the operation should be preceded by transfusion if the bleeding has been at all alarming

It is in this group of younger patients in whom more radical and more certain measures are contra indicated that we have our great field for such organotherapy as is now available Radiologists agree with

gynecologists that radiotherapy should, as far as possible, be avoided in patients of this group, even in carefully controlled doses designed to check the menstrual function only temporarily In the occasional intractable case such regulated radiotherapy may be justified, though *most gynecologists probably would prefer occasional repetition of* curettage Some ovaries are singularly sensitive to the effects of radium and x-ray, and I have personally observed a number of instances in which even small dosage in the hands of expert radiologists has been followed by permanent abolition of ovarian function Moreover, there is still no unanimity as to the effect of such treatment upon future pregnancies, particularly with reference to the possibility of defective offspring

Organotherapy—From what has been said as to the incompleteness of our knowledge of the pathological physiology of uterine bleeding it is not surprising that the organotherapy still is far from satisfactory It is based chiefly on the concept that the bleeding is due to relative excess of estrogen and lack of progesterone, and it aims chiefly to increase the progesterone or to lessen and counteract the estrogen The following organotherapeutic plans may be discussed in summarizing fashion

(1) *The use of the chronic or anterior pituitary-like hormones of pregnancy urine* The original employment of these substances was based on the hope that the pregnancy urine hormone principles might produce luteinization in the human ovary as they do in the ovaries of experimental animals, thus supplying the lacking hormones It should *be remembered that, when this clinical experiment was made* progesterone itself was not available for clinical use Histological studies of the ovaries of treated women soon established that the desired luteinization was not produced, but the fact remains that many clinicians have reported good results in a certain proportion of cases On the other hand, no one can claim consistent or highly satisfactory results, nor has anyone been able to explain how such substances exert their effect It has seemed to me that a larger proportion of cases respond to these pregnancy urine preparation than to progesterone itself, especially when the latter is used in small dosage When these preparations are used, the usual plan is the hypodermic injection of doses of 200 to 500 units daily with the onset of bleeding, continued until bleeding is controlled, or until six or eight injections are given If free bleeding persists beyond this, not much is to be expected from further injections and other plans of treatment should be resorted to

(2) *The use of progesterone* This hormone is readily available com

mercially though still quite expensive in the dosage often indicated in the treatment of functional bleeding Certainly no one would expect to bring about secretory changes in a proliferative type of endometrium with doses of from 1 to a few milligrams daily for a few days and the many reports of good results with such dosage are better explainable by the assumption that the disordered bleeding mechanism is influenced by much lower dosage than is required to bring about histological changes in the endometrium This is in accord with what has been said in a previous paragraph as to the different thresholds of hormone sensitivity of the various endometrial functions

(3) *The use of testosterone propionate* The effect of the androgenic hormones upon the female cycle has been studied much during the past two or three years and there still is much that is not clear Almost all investigators believe that the effect upon the growing follicle is an inhibitory one and that thereby estrogen production and endometrial proliferation are lessened There is evidence too that in the progestational phase of the ovulatory cycle the effect of progesterone is supplemented and enhanced by the androgenic principle

It is not surprising that the male sex hormone substance in the form of testosterone propionate has achieved much recent vogue in the treatment of functional bleeding At the outset I may say that in my hands it has yielded more satisfactory results than either progesterone or the pregnancy urine preparations During the bleeding phases it may be given intramuscularly in doses of 10 mgm three times a week and in the more severe cases 25 mgm twice a week Much larger doses are used by some but I believe that this tendency should be avoided A number of reports have been published of hirsutism and occasionally other masculinization phenomena such as change in voice Such symptoms apparently disappear with withdrawal of the drug though very slowly

In any event such sequelæ are highly undesirable and if they were at all common most of us would no doubt feel that the use of testosterone scarcely would be justified I do not believe that the use of the moderate dosage I have suggested is attended with any worthwhile risk of such unpleasant symptoms especially if giving it is avoided in patients who already show a tendency to hirsutism or excessive pigmentation The best policy is to avoid the larger doses and rarely to give more than 50 mgm a week especially when as in cases of functional menorrhagia the hormone is kept up throughout the cycle It behooves all of us in these early days of testosterone therapy to be constantly on the alert for

undesirable by-effects, such as those I have mentioned, until further experience enables us to evaluate more intelligently the safety or the hazard involved.

(4) *The use of thyroid extract.* In only the occasional case of functional bleeding does hypothyroidism appear to be a factor, but when it is, thyroid therapy is indicated and is likely to be curative. Recently I have observed a striking case of this sort. The patient was a woman of 32, who for several years before I saw her had been taking huge doses, gr. 20 (1.3 gm.) a day, of thyroid extract with no evidence of saturation symptoms and with a basal metabolic rate still slightly on the minus side. If this dosage was stopped or markedly lessened, profuse menorrhagia always would appear, with return to a normal menstrual amount with the resumption of the thyroid. In the overwhelming majority of cases of functional bleeding, however, no thyroid element appears to be concerned and thyroid therapy is of no value.

The Use of Estrogens.—Until recent years the estrogens were rarely resorted to in the treatment of functional bleeding. It was generally thought, as it still is, that the bleeding phases occurred, when the estrogen level dropped below a certain point, which quite surely differs very widely in different individuals and different species. It seemed logical enough to believe that by raising this estrogen level the bleeding might be checked at least temporarily, and many of us for many years have at times resorted to this plan.

The method can be carried out in various ways. The simplest plan, *in the case of bleeding known to be of functional nature, is to give* a daily large oral dosage, ordinarily 8 to 10 mgm. of diethyl stilbestrol, until the bleeding is checked, as it will often be within a very few days. If the stilbestrol, to use the common commercial designation, be then suddenly stopped, bleeding is likely to return, but if the withdrawal is gradual, lessening the dose 1 or 2 mgm. a day, there is either no return or at most only a slight bleeding. With the return of another bleeding phase which continues more than a reasonable number of days or is very profuse, the large doses of stilbestrol are again resumed with later decrease as described above.

In the milder forms of functional bleeding this simple plan often will tide the patient over until the hoped for endocrine re-adjustment occurs, as it not infrequently does. The stilbestrol in such cases exerts its hemostatic effect by correcting the low estrogen level which apparently is the immediate cause of the bleeding. Nor are the rather large doses employed in any way harmful, although a certain proportion of

patients probably 10 to 15 per cent cannot tolerate them because of unpleasant side effects such as nausea and vomiting If such effects are encountered the natural hormones may be used in correspondingly large hypodermic or oral doses or more often one of the other oral estrogens may be employed such as hexestrol premarin benzestrol dienestrol meprane or ethinyl acetate (estinyl)

In some cases better results may be obtained by keeping up the large doses of estrogen for about three weeks Bleeding ordinarily will be checked recurring 5 or 6 days after the last dose After a few days the estrogen is again resumed but smaller doses of these control the bleeding

Cyclic Therapy —Estrogen treatment helpful as it often is is superficial in the sense that it is directed toward the immediate ovarian dysfunction rather than to the underlying pituitary disorder although in some cases the latter appears to right itself whether spontaneously or as a result of the treatment Hamblen and Smith are warm advocates of cyclic methods of treatment employing the estrogen and progesterone feeling that these offer a better chance of inducing a re adjustment of pituitary function Hamblen after preliminary control by large doses (6 mgm) of diethyl stilbesterol somewhat after the plan above mentioned keeps up the dosage for 20 days Its withdrawal is followed by bleeding after an interval of 1 to 5 days On the fifth day of this withdrawal bleeding 3 mgm of diethyl stilbestrol is begun again in daily doses for 20 days with a third cycle of stilbestrol later somewhat according to the same plan On the fifth day of the withdrawal bleeding following the third cycle of estrogen therapy 3 mgm doses of stilbestrol are again started and kept up for 20 days but during the last 10 days of this series 10 mgm of progesterone is given intramuscularly every day or 30 or 40 mgm of anhydro-hydroxy progesterone are given orally and daily For patients who fail to respond to this plan he suggests a trial of what he calls one two cyclic gonadotrophin from the 5th to the 14th days of the cycle followed from the 15th to the 24th days by daily intra muscular injections of chorionic gonadotrophin

It is obvious that the expense of such treatment will make it prohibitive to many patients while the inconvenience of daily injections for long periods of time will make many feel that the remedy is worse than the disease especially as there is no certainty of benefit Nor does the supposed rationale of this elaborate plan appear to all of us as unimpeachable It appears to be based on the concept that either by ovarian

or gonadotrophic therapy it is possible to beat the pituitary into a sort of cyclical submission, a very uncertain hope with a sick and poor reacting gland It would seem just as logical to try to convert anovulatory into ovulatory cycles by the simple expedient of supplementary progesterone therapy, a rather fatuous ambition in the present state of our knowledge

The objections expressed to Hamblen's plan apply also to the elaborate and expensive ritual outlined by Smith, especially in the case of women who have more or less continuous bleeding He recommends that "10 mgm of progesterone and 1 mgm of estradiol should be injected on the first day of treatment and 10 mgm of progesterone daily for the next 4 days The bleeding probably will be controlled by the treatment, and a fairly normal period will occur 2 to 4 days later Counting the beginning of this period as the first day, the same course of injections is repeated beginning on the twenty-first day This course of treatment should be given at least twice and may be repeated again after an interval, if there is any recurrence of excessive bleeding If the bleeding is profuse, the daily dosage of progesterone is increased to 50 mgm, reducing the dose as the bleeding becomes less but continuing injections for at least 5 days or longer, if necessary to control the bleeding" Following this formidable and highly expensive preliminary treatment cyclic therapy then is begun Even if the plans were always successful, which it is not, I cannot conceive that many patients would be willing to submit to it especially if they have to pay for all the progesterone employed Nor is it as yet certain that it is any more effective than some of the plans discussed previously For that matter, in the occasional very intractable case, I would prefer to resort if necessary, to an occasional curettage especially as this can be performed so readily without hospitalization and with no anesthesia where the suction curettage is done, or with a light sodium pentothal anesthesia if the customary technique is employed Almost always this is followed by at least temporary relief from the bleeding

Other Methods—All the methods thus far discussed are directed largely to the ovarian manifestations of a disorder involving the pituitary with the hope that the latter will be indirectly influenced by the ovarian therapy A more direct pituitary approach is attempted by the employment of the various *gonadotrophic preparations* which have been used, such as the equine gonadotrophic principle or as previously mentioned the chorionic gonadotrophic hormone I do not believe that any one

will maintain that thus far these have yielded any conspicuously good results and it seems hardly worthwhile to discuss them here

The fact remains however that of all the numerous cases of functional bleeding encountered by every gynecologist there is only a small proportion which are so severe and so intractable that more radical measures such as light radiotherapy in small dosage or even hysterectomy have to be thought of

Certainly there would be little reason to criticize the employment of *light radium dosage* not exceeding a few hundred mc hours in the occasional patient of the younger group who has proved intractable to more conservative measures but the plan is not without hazard as some ovaries are singularly sensitive to even light radium dosage and even permanent abolition of the function may ensue Other ovaries on the other hand are quite resistant so that the effect of the mild doses ordinarily considered safe is difficult to predict Other objections have been urged such as the possible effect of such therapy upon subsequent generations of ova although it must be admitted that the evidence on this point is not by any means convincing In general however most gynecologists will look upon radiotherapy in young women as a method not to be resorted to unless the various plans of endocrine therapy have proved ineffective

Psychological Management —In treating functional bleeding especially in young women I think it a wise psychological approach to explain to the patient the difficulties and uncertainties of our present day methods and the possibility that she may be in for a career of disagreeable bleeding and therapy of unpredictable length but to encourage her by urging that sooner or later perhaps within a few months but perhaps not for several years she has an excellent chance of becoming essentially normal With such explanations the patient is likely to be cooperative in treatment appreciating the desire of the doctor to cure her without resort to radical procedures

General Measures —I need not here elaborate on the fact that whatever method of treatment is employed for the disorder itself general measures are not to be neglected In the milder forms anemia may not be a problem but in those of more severe grade it always is so that hematinics and transfusions often are indicated When transfusion is done it is a great advantage when it is practicable to use blood from a pregnant woman because of its high gonadotrophic content This is of double value not only making up the blood loss but having a beneficial effect upon the bleeding

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periods, obviously with some form of ovarian hormone. These rough figures of course do not constitute an accurate index of the varying degrees of severity of menopausal symptoms, for many other factors are concerned, not the least of which is the enthusiasm or lack of enthusiasm of the medical attendant for endocrine therapy.

As to the second point, it may be asked what are the characteristic symptoms of the menopause. With reference to only one group will there be general agreement. I refer of course to the well known vasomotor phenomena, especially the periodic flushes and sweats and, though less frequently noted, the flashes of heat which may involve the whole body. *This is not to say that somewhat similar phenomena may not be due to other factors than the menopause, for they are seen not rarely in certain cases of hyperthyroidism, and they may be even more simulatory in the nervous syndrome commonly spoken of as "vasomotor instability," often encountered in middle aged women and mimicking* either the menopause or hyperthyroidism. The latter especially may be imitated quite perfectly, as tachycardia is often a prominent symptom though the basal metabolic rate is normal. It is the latter group of cases which surgeons have learned to shy away from, for thyroidectomy does no good and may do harm.

In spite of these relatively rare exceptions the fact remains that vasomotor flushes and sweats in the woman of menopausal age, especially when menstruation is becoming scantier, less frequent, or has ceased altogether, usually may be assumed to be the direct result of the endocrine readjustment characterizing this phase of life, but they are not so clearly objective as, for example, the symptoms following extirpation of the thyroid or parathyroids or those associated with tuberculous destruction of large areas of the adrenals. The psychic hook-up of the menopausal hormone factors primarily concerned seems much more intimate, so that the severity of the vasomotor phenomena may be influenced much by the patient's psyche. This not only makes it difficult to evaluate the results of organotherapy, but at the same time clearly indicates that organotherapy is only a part of the management of the menopause.

It is surprising that there has been so little discussion, much less study, as to the mechanism of the menopausal vasomotor phenomena. The brilliant advances made in reproductive physiology have added little to our knowledge concerning this question. No other animal, so far as we know, exhibits similar phenomena, so that the experimental approach through the study of lower animals appears to be blocked.

The Menopause and Its Management

The popular concept of the menopause, as is true of all aspects of the phenomenon of menstruation, has been based on folk lore rather than on scientific fact, of which there was little until recent years. There is now, however, a growing appreciation of the fact that the "change of life" does not usually entail any very profound alteration in the woman's life current except that depending on the cessation of menstruation and on the reproductive function. The term "climacteric" would seem a more expressive one for this phase, derived as it is from a Greek word meaning 'rung of a ladder' and indicating, therefore, merely that it represents one of the natural transitional steps which inevitably must be taken by every woman on her progress from the cradle to the grave, provided she lives long enough.

As a matter of fact there are many women to whom the menopause comes as a boon with striking improvement in general health and well being, even apart from the elimination of the physical and mental stress which often are entailed by repeated child-bearing and the cares of rearing perhaps many small children. The cessation of the menstrual function, associated as it often is with an increase in weight, has converted many an unattractive thin worried woman into the graceful and serene type of matron, veritably a second flowering.

While it is true that the subjective symptoms of the menopause are in the aggregate potentially more disturbing than those marking the inauguration of the menstrual function, two facts may be considered as clearly established: (1) that in only a small minority of women are the characteristic menopausal symptoms sufficiently severe to interfere materially with health and happiness as measured roughly by the necessity for medical attention, and (2) that many of the symptoms often complained of by women in the fifth decade of life are attributable wrongly to the menopause.

The first of these statements needs no great elaboration. Some time ago I questioned on this point 100 patients who had passed through the menopause and who represented various social types, so that they might perhaps be considered a fairly cross sectional group. Without going into details suffice it to say that in 72 of this group the menopausal symptoms had not impelled the patients to seek medical help. In 20 there had been treatment with preparations of one sort or another by the oral route, presumably either glandular substances or simple nerve sedatives. 8 patients had been given hypodermic treatments for varying

bleeding of the menopause seem as a group to exhibit relatively mild degrees of vasomotor disturbance

As already stated the occurrence of the menopause is associated characteristically with the appearance in the urine of considerable amounts of the pituitary gonadotropic factors especially the one concerned with *follicle ripening* Indeed it was thought formerly that only this latter of the pituitary sex hormones was to be found but Frank and Goldberger were able to demonstrate the occasional presence of the luteinizing factor as well

There are some like Albright who believe that the vasomotor menopausal symptoms are due rather to the gonadotropic excess than to the estrogen deficiency but more and more the evidence indicates that it is the disruption of the previously existing quantitative balance between the hypophyseal and ovarian functions which is responsible for any menopausal clinical upset and that the prime factor in this is the withdrawal or lessening of the ovarian secretion Many investigators have shown that the administration of sufficiently large amounts of estrogen brings about disappearance of the gonadotropic factor just as withdrawal of the ovarian secretion increases gonadotropic activity

The administration of estrogenic substances in women suffering with undoubted menopausal symptoms is strictly in accordance with present day physiological knowledge This is true whether such therapy is carried out in a purely substitutional way with the idea of easing the hormonal adjustment and making it more gradual or whether it is resorted to with the avowed object of bringing about a lessening of the gonadotropic overactivity of the pituitary

Aside from the vasomotor phenomena which I have been discussing a whole legion of others have been ascribed to the menopause while in the minds of the public almost any symptom that happens to occur in the middle aged woman is apt to be explained by the change of life In this connection I wonder whether many of our colleagues are not at times to blame in suggesting to the woman or in acquiescing in her own ready suggestion that the menopause is responsible for all sorts of indefinite symptoms especially when a more likely cause for the latter is not patently clear

A distinction should be made between (1) those symptoms which are clearly menopausal in origin in the sense that they are the physiological results of the cessation of ovarian activity and ( ) those frequently seen in women passing through the menopause but only indirectly or secondarily of menopausal origin and therefore not characteristic

The very nature of the vasomotor flushing its distribution and its apparent kinship to the phenomenon of blushing suggest that the immediate factor is the vasomotor nerve apparatus and that behind this are stimuli from the higher areas of the brain The obvious implication is that there are points of contact between the hormonal and cerebral pathways, for which indeed there is evidence in other phenomena as well

As bearing on the problem under discussion it would seem that recent investigations pointing to the probable existence of a rhythmic sex center at the base of the brain presumably in the parahypophyseal area and quite certainly hooked up with the hypophysis itself offers the logical hint as to the location of the psychoneurohormonal liaison concerned in the vasomotor disturbances of the menopause It is much too early however, to consider this as established, especially as we are entirely ignorant as to the mechanism or the pathways concerned

As regards the hormonal readjustments of the menopause it seems clear that these are initiated by failure of ovarian function and that this is due to a natural limitation of the ovary's physiological life span It has not been possible in postmenopausal animals to reactivate the ovary by any form of pituitary injection or implantation Westmann alone claimed to have brought about in this way the production of corpora lutea in postmenopausal ovaries, but his results have not been supported by other observers

According to Zondek the hormone picture presents differing aspects at different phases of the menopause There is first a period during which estrogen is present in excessive amount hyperfolliculinism, then one in which there is a deficiency of this hormone hypofolliculinism and finally a phase continuing on for many years, in which the gonadotropic pituitary hormones are present in excessive amount This final phase Zondek spoke of as polyprolanism though now the term prolan commonly is limited to the anterior pituitary like substances found in the urine of pregnant women and more properly spoken of chorionic hormone

There is no doubt from the work of various subsequent investigators that the hormonal picture of the menopause is really a kaleidoscopic one, and that the sequence of events originally described by Zondek is not the invariable one

It is during the stage of estrogen excess that one is most apt to have menstrual excess though there are many exceptions to this It is of interest to note however that women who suffer with functional

bleeding of the menopause seem as a group to exhibit relatively mild degrees of vasomotor disturbance

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To illustrate what is meant, let us take the example of an average uninformed woman who approaches the menopause with a considerable degree of apprehensiveness. The occurrence of frequent hot flushes and sweats, often disturbing her rest at night and awakening her with a panicky feeling, increases her nervous instability and makes her irritable. Why should not such a woman have headaches, a tendency to insomnia, loss of appetite and other digestive symptoms or any of many other subjective manifestations? These are certainly not the direct results of any endocrine disturbance, but they are a part of this particular woman's menopausal disturbance.

A similar mixture of direct and indirect menopausal symptoms is seen in milder degree in many women, while in a very large number both the primary and secondary manifestations are of such insignificant degree as to constitute no problem whatever.

Although the hormonal etiology of the vasomotor phenomena is accepted universally, this does not mean that other menopausal symptoms such as headache, vertigo and irritability may not, in some cases, be direct results also of the same cause, but with these subjective symptoms it is much more difficult to establish such a direct relationship, especially as they are associated so commonly with functional neuroses; hence the hazard of utilizing them as criteria of treatment.

In our management of menopausal women, therefore, we deal only in part, often in very small part, with clear cut and direct manifestations of endocrine disturbance, and the practitioner looking only for these and disdaining all others often will fall far short of the requirements in the individual case. The best results undoubtedly will be obtained by the physician who knows something of gynecology and endocrinology, but who is above all a doctor with common sense, which almost includes the additional requirement that he be something of a psychiatrist. There are wide variations in character and degree of the symptoms presented by menopausal women, depending not only on the severity of the hormonal readjustment but also on such factors as the patient's psychic make up, her social, intellectual and economic status, her family life and her general physical condition. The method of approach must therefore be adapted to the individual case but should always be combined with sympathetic understanding and reassurance and a patient effort to discover, evaluate and adjust such factors as I have mentioned.

While we cannot in practice always sharply separate the direct hormonal symptoms from those which are indirect, it is the former which must serve as our chief guide to organotherapy. The history of

gland treatment of menopausal disorders is amusing or pathetic, depending on the point of view. From the time of its first introduction at the old Landau clinic in Berlin in 1896 there has been wide divergence of opinion as to its efficacy. The practice began even before it was known that the ovaries have any secretory function, and we now know that the preparations so widely used until recent years (ovarian or corpus luteum tablets or capsules or ovarian residue) were practically inert. And yet many clinicians had convinced themselves of the value of such treatment. For example, the late Dr. William P. Graves, an able clinician, honestly believed and stated that corpus luteum therapy is "almost a specific" in the treatment of menopausal symptoms, referring to the oral use of corpus luteum preparations now known to contain little or none of the active hormone.

Now that we have available for clinical use preparations of the ovarian hormones which are unquestionably active from a laboratory standpoint, one important factor of uncertainty has been removed, but others still remain. In evaluating results the proper standard should be the effect obtainable on the vasomotor phenomena and not on the host of other questionable symptoms often seen in menopausal women, as so many writers have done. The effect on the vasomotor symptoms can be studied with at least a measure of objectiveness, as has been done by various observers (Novak, Howard and Everett), and the results seem to justify this form of therapy quite clearly.

The duration of treatment is to be adapted to individual indications. Menopausal symptoms are rarely persistently troublesome, and it is usually only during exacerbations that active hypodermic medication is necessary, and only a few injections may be required. In the intervals the patient may need no medication or at the most the administration of some simple sedative of the bromide or barbituric acid group.

A valuable new addition to our armamentarium in the treatment of menopausal symptoms has been made through the discovery that certain non-hormonal chemical substances exhibit high degrees of estrogenic potency. The best known of this group of substances is the stilbene derivative known as stilbestrol, which some years ago became commercially available after a long preliminary period of clinical trial in many clinics. Aside from its great potency, stilbestrol has the great advantage of being relatively inexpensive and of being very effective when given orally, so that it now enjoys wide popularity.

Its chief disadvantage is that it produces unpleasant toxic symptoms such as nausea, vomiting, gastric irritability and vertigo in a proportion

of cases which varies in the reports of different clinics but which averages about 15 per cent These symptoms are not serious and they disappear with withdrawal of the drug but they make its use difficult in a small proportion of cases More dangerous toxic symptoms have not been noted, even after long continued administration There appears to be little difference in the degree of potency by the oral and hypodermic routes of administration so that the former is much the more popular The unnecessarily large doses formerly employed by some up to 25 mgm daily have been abandoned and there is general agreement that rarely should the daily dose exceed 1 mgm, and that usually it may be much lower Nor is it necessary to keep up the use of the drug constantly in view of the fact that menopausal symptoms are so often intermittent When severe, a daily dose of 0 5 mgm will often, after a number of days bring about such amelioration that the dose may be reduced or omitted altogether In the occasional severe case a larger dose may need to be continued for a somewhat longer time A disadvantage of the drug in some cases is that it has a greater tendency than do the natural hormones to bring about uterine bleeding and thus lead to a suspicion of some such intrauterine lesion as adenocarcinoma However if the substance is used circumspectly this is a relatively infrequent occurrence

When stilbestrol can not be easily tolerated as is the case in from 10 to 15 per cent of women there is available a considerable group of other oral estrogens hormonal and non hormonal with a much lesser degree of toxicity Among them may be mentioned hexestrol dienestrol premarin meprane and estinyl Hypodermic medication is practically never necessary and should always be avoided because of the hazard of producing a psychological shot addiction Another common and pernicious abuse is to put the patient on persistent so-called maintenance, estrogenic dosage Aside from the risk of thus producing postmenopausal bleeding such therapy actually prolongs the menopause by keeping up a substitutional ovarian function

A question which has been much discussed is as to whether or not estrogenic therapy, which has its greatest field in the treatment of menopausal symptoms is associated with any hazard of inciting the development of cancer This fear is based largely on the fact that in some of the lower animals it has been possible to produce cancer-like lesions of the breast or uterus after prolonged administration of very large doses of estrogen far larger than would ever be employed therapeutically The question is too large to discuss in all its ramifications Suffice it to

say that aside from a very small and unconvincing group of human cases in which cancer has developed later in women who had received estrogen therapy there is no evidence that the customary therapeutic dosage of the estrogens carries with it any carcinogenic hazard Certainly it would in the present state of our knowledge be unjustified to deprive a woman of the benefits of estrogenic therapy merely on this basis On the other hand until we know more as to the actual status of this question it would seem discreet to be cautious in the employment of estrogens in women in whom there would seem to be a strong familial predisposition to cancer or who are suffering with any type of lesion which might be considered to be of so called pre cancerous character

Endocrinopathic Sterility

Certainly a not inconsiderable group of cases of sterility is explainable on an endocrine basis but unfortunately we know very little in most instances as to the endocrine factors involved In some the sterility is associated with amenorrhea so that the explanation and the treatment are identical with what has been said concerning the latter Where there is definite evidence of hypothyroidism thyroid therapy is indicated clearly This is the most favorable group so that the clinician usually is rather grateful when he receives a report that the basal metabolic rate is far below normal

Another type of endocrinopathic sterility is represented by those patients in whom ovulation does not occur even though menstruation is quite or nearly normal These anovulatory cycles occur most frequently in very young women and those approaching middle life though they may occur at any age Their age incidence in other words is identical with that of the so called functional bleeding which likewise is associated with the absence of ovulation and therefore sterility

Can anything be done to correct these? Unfortunately we do not know what endocrine factors are esssential for ovulation though the available evidence indicates that a certain quantitative balance between the two pituitary sex hormones determines the occurrence of the phenomenon Since this balance differs in different species, the problem of producing ovulation in the human being with our available knowledge and methods seems rather hopeless for the present To rupture the follicles by bimanual pressure as has been suggested by some would would not be altogether without hazard and probably would not be

successful, as it is quite sure that, in the absence of the proper endocrine setting, the ovum would not be capable of fertilization and that follicle rupture would not be followed by luteinization and corpus luteum formation For the present the best plan, admittedly inadequate, seems to be to do everything possible to correct the constitutional and endocrine status of the patient, to give small doses of the inevitable thyroid and perhaps to administer the so-called equine gonadotropic hormone preparations during the usual ovulation span inasmuch as in animals, at least, these substances are capable of inducing ovulation For the details of such treatment, as well as of the methods of study so often called for by the difficult problem of sterility, the practitioner usually will involve the assistance of the gynecologist

In spite of the uncertainty as to the method of its action thyroid therapy quite generally is believed to be much more frequently successful in the treatment of endocrine sterility than any other substance It seems very likely, though there is no proof on this point, that its influence is exerted on the quality of the germ plasm The doctrine of "defective germ plasm" as a cause either of sterility or habitual abortion is now accepted by the best and the most conservative embryologists, and it seems likely that this is the factor which may be influenced by thyroid treatment The recent interest in the use of vitamin preparations, such as the germ-oil products, evidently is based on a supposed effect on similar lines though as a recent report of the Council of Pharmacy and Chemistry of the American Medical Association indicates, there is no reliable evidence on this point as yet

Finally, in the consideration of endocrinopathic sterility, it should be emphasized that a search for endocrine factors in the husband is just as important as in the case of the wife

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CHAPTER XIX

DWARFISM

By ARTHUR GROLLMAN

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Definition —A dwarf may be defined as a diminutive human being (Webster) The human stature is exceedingly variable and hence it is difficult to assign limits of normal growth Anthropologists[6] have adopted 130 and 122 centimeters as the lower limits of stature of the adult male and female respectively Individuals who at maturity fail to attain these heights are considered to be dwarfs However the term dwarfism usually is applied clinically to include all individuals who are merely stunted in growth and undersized in stature as compared to individuals of the same age sex and racial stock even if their height exceeds that adopted by anthropological standards

Except in the case of the true dwarf described under the heading Primary Dwarfism in whom the abnormality in stature is the primary disorder dwarfism is only a secondary manifestation of some disorder of chondral or osseous development endocrine disturbance metabolic disease etc It is the demonstration of the stigmata associated with these disorders which justify the application clinically of the term dwarfism to a given individual rather than the abnormal stature per se

A reduction in stature need not necessarily be pathological as for

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importance of the kidney in the pathogenesis of the disorder considering it merely as a manifestation of delayed rickets It was not until 1920 that Barber indicated clearly the relation of the renal involvement to the skeletal changes and designated the condition as renal rickets

The Nature of the Growth Process

Dwarfism is a manifestation of the failure of the normal growth process. The tendency to grow is a fundamental property of living matter but the nature of this inherent impulse is unknown All the variable factors to which the cells are subjected influence their growth but there remains some inherent constitutional factor which stimulates growth and which limits the extent to which it proceeds This inherent property of the cells and its independence of the environment is demonstrated in hetero plastic grafts where as Harrison[8] has shown the limbs of two species of different size respond according to their inherited growth capacity rather than to the growth pattern of the species upon which they are implanted Racial type although rather obscured in the human species and the familial tendency thus are important in evaluating the degree of normality of stature in a given individual

In the vertebrate skeletal growth plays a primary role in determining the ultimate size of the individual as a whole as well as of his separate parts Thus in certain of the lower vertebrates fishes amphibia growth continues for many years at a fairly uniform rate In mammalia e g the rat where the epiphyseal cartilages remain open growth continues throughout life although at an increasingly slower rate following maturity In the human also growth may proceed at an advanced age if the epiphyses have not closed while the pinna the supporting tissue of which is cartilage continues to grow for years after skeletal growth has ceased The form of dwarfism to be described subsequently as primary involves a defect in the constitutional growth process whereas most other varieties of dwarfism observed clinically are due primarily to an interference with osteochondral growth

The rate of growth is not uniform but undergoes wide variations depending upon the sex the environment and the heredity of the individual Three definite peaks of the growth curve are recognizable normally the first year of post natal life the fifth to eighth years and the period of adolescence In the female the rapid period of growth during adolescence tends to start sooner and terminate earlier and is less intensive than in the male[19]

Linear growth occurs at the epiphyseal cartilages new bone being

example in the pigmies of Africa and Australia in whom this occurs as a normal characteristic of the race It is erroneous to refer to the pigmies as dwarfs for they exceed 140 centimeters in height Their growth merely is slowed but otherwise normal in every respect[6]

Dwarfism is to be differentiated from infantilism in which the characteristics of childhood persist beyond adolescence without there being *necessarily any retardation in stature Infantilism accompanies many* types of dwarfism but it may be present in individuals of normal or excessive height as in eunuchoidism In many dwarfs primary and achondroplastic on the other hand infantilism does not occur sexual and mental development being entirely normal

History

Dwarfism like its counterpart gigantism has attracted attention from the earliest times of recorded history The Egyptian god Bes depicted as a bearded achondroplastic dwarf[41] was worshipped first as a deity who averted omens of witchcraft and later as a god of pleasure ruling over the *realm of sexual intercourse childbirth singing and dancing* In the Graeco Roman world a replica of Bes was worn as an amulet a custom which continued until the middle ages The Egyptian god Ptah is represented also as a typical achondroplastic dwarf In mythology and folklore dwarfs have been represented on the one hand as skillful and helpful artisans on the other, as mischievous elfs

During medieval times dwarfs frequently were maintained as jesters and royal retainers The painters Holbein van Dyck and Velasquez have left us notable portraits of famous dwarfs of their time

It was not until the latter decades of the nineteenth century that the study of dwarfism was put on a scientific basis Lorrain in 1871 described dwarfism with genital underdevelopment which as the Lorrain Levi syndrome subsequently was associated with pituitary infantilism although as originally described the syndrome includes many instances not due to hypophyseal deficiency The relation of the pituitary to dwarfism was defined clearly by Erdheim[16] in 1916 who designated the condition as *nanosomia pituitaria* utilizing a term nanosomia introduced by Virchow to include both dwarfism and infantilism[2] Parrot in 1878 first established the achondroplastic dwarf as a definite entity the pathology of which was described clearly by Kaufmann in 1893 who designated the condition more accurately as chondrodystrophia fetalis

The first description of the condition now designated as renal dwarfism was given by Lucas in 1883 However Lucas failed to appreciate the

certain therapeutic measures are available for increasing the stature in some forms of dwarfism knowledge of the etiology of the fundamental disorder responsible for the limitation of growth is desirable

The dwarfs encountered clinically may be classified into the following five groups (1) primary dwarfism (2) dwarfism due to osteochondral malformations (3) renal dwarfism (4) dwarfism of endocrine origin (5) dwarfism due to metabolic and cachectic disorders

This classification lacks absolute rigidity Renal dwarfism for example is due to osseous malformations secondary to renal disturbances and hence might be included under (2) or (3) while cases of juvenile osteitis fibrosa cystica usually classed with the renal dwarfs actually are of endocrine origin The simple classification given has nevertheless the advantage of convenience as compared to more detailed and complex systematizations As will be seen later certain general clinical features characterize each of the groups mentioned and recognition of the class to which the patient conforms is the first step in diagnosis

In general we may divide dwarfs into two general class s (1) primary and (2) secondary In the former are included the true dwarfs or midgets in whom small stature occurs in an otherwise normal individual The primary defect in these patients is one involving the growth process only All other cases of dwarfism owe their origin to some fundamental defect metabolic endocrine or osseous in origin which with other manifestations results in retarded stature The dwarfism in these cases is secondary to the primary disorder

The group that has just been designated as secondary dwarfism includes a number of disorders Dwarfism in this group of patients is only one manifestation of disease It may represent the major deficiency as in achondroplasia or be of relatively minor import as it is for example in cretinism

PRIMARY DWARFISM

Definition — By primary dwarfism we refer to the true dwarf or midget This form of dwarfism has been designated also as *true* or *essential* and as *ateleiosis* The last named term indicates incomplete development but also connotes infantilism Its use in association with this type of dwarfism would therefore seem less accurate or exact than the designation primary

Like their counterpart the giants these dwarfs have always been the subject of curiosity The famous Tom Thumb publicized by Barnum was an example of this form of dwarfism as are also many of the midgets

added at the diaphyses of the long bones and at the surfaces of the vertebrae The growth activity at the different cartilages however varies thereby altering the body proportions This is important in analyzing the growth abnormalities observed in dwarfism In the infant the limbs are short compared to the trunk the distance between the symphysis and vertex compared to that between the symphysis and soles gradually decreasing with age The length of the head compared to that of the body which in the adult is as 1 8 is only 1 4 in the infant Other body measurements frequently utilized in evaluating disproportion in dwarfism are the distances from the crest of the ilium to the symphysion or the most anterior point of the alveolar process of the mandible which more accurately defines the size of the trunk than does the distance to the vertex and that of the crest of the ilium to the soles or more conveniently to the malleolus

The endocrine organs influence the growth of the osteochondral system as well as that of the rest of the soma This should be looked upon as an effect of the endocrine secretion on the tissues generally rather than upon the growth process specifically as is usually done Thus the pituitary cannot accurately be considered as a regulator of growth since this may proceed in the absence of pituitary secretion The abnormalities of growth observed in endocrine disorders are only one aspect of the dysfunction induced by lack or overproduction of the hormones on the metabolic processes generally This will be discussed more fully in a subsequent section

Chronic illness protracted infections parasitic infestation metabolic disturbances avitaminoses malnutrition and in general any condition affecting the general health of the individual may limit growth This process involves the growth cartilages which under adverse conditions cease to proliferate and even may become calcified [7] The socio economic condition of the individual and his general health during childhood thus are important determinants of his ultimate stature

Classification

It is evident from the preceding section that dwarfism may be due to many causes and that any system of classification is intended solely as a matter of convenience A number of classifications have been devised by different authors based on etiology or body form[19] The literature has been confused by the use of eponyms or descriptive terms purporting to indicate some particular form of dwarfism but many of these must be discarded as not representing any distinct clinical entity Inasmuch as

physeal cartilages such as is observed in the hypothyroid dwarf[13] The epiphyses remain open at advanced age and the centers of ossification often are infantile and at times supernumerary In the 11 dwarfs of Ecke s series[13] whose average age was 29 years the bone age as determined roentgenologically was only 13 years[13] The nasal sinuses are juvenile in their appearance in the x ray The head of the femur may be affected and resemble that observed in Perthe s disease[13]

Treatment

No attempted form of therapy has been successful in modifying the growth defect in primary dwarfism Endocrine preparations thyroid pituitary are ineffective as indeed might be anticipated from the perfectly normal nature of the dwarf s own endocrine system Use of excessive doses of dessicated thyroid would be expected to induce symptoms of hyperthyroidism while pituitary extracts if available in sufficiently potent form might induce acromegaly as they do in the normal adult Since the epiphyses are not closed growth may continue for many years usually at a very slow rate

Intermarriage of primary dwarfs is of common occurrence among circus midgets The children of such couples may b normal but there is insufficient data available to determine the incidence of dwarfism in the offspring of such matings

Dwarfism due to Primary Osteochondral Malformations

Defects or malformations of either the cartilages or bones may result in skeletal deformities which if extreme may lead to dwarfism Certain of these deformities are congenital in origin others are acquired during early life In the present section will be considered those forms of dwarfism which are due to conditions considered to be primary osteochondral malformations and not secondary to the endocrine avitaminotic metabolic or other disturbances which are discussed later

Chondrodystrophia Fetalis Achondroplastic Dwarfism

This condition is the principal cause of dwarfism Although commonly designated as achondroplasia the disorder actually is a dystrophy of the growth cartilage and hence the term chondrodystrophy more correctly designates the condition Because of the shortened extremities characteristic of the disorder it has been designated also as *micromelia achondro*

Etiology

The exact cause of this variety of dwarfism is unknown The condition may be hereditary for it commonly affects several siblings Thus in 4 families reported by Ecke[13] 14 of the children were midgets and an equal number of normal size The parents in two instances were consanguineous There is apparently some defect in the germ plasm which is responsible for the failure of growth to proceed to its normal limitations There is no reason to believe that primary dwarfism is due to any metabolic disorder or to maldevelopment of the osteochondral system nor is it likely that the condition represents simply an extreme in the normal physiological variation of statural attainment[76]

Pituitary insufficiency has been held responsible for this disorder due to the finding in some cases of cystic degenerative changes in this gland[11] It is questionable however if these were not actually pituitary dwarfs rather than cases of primary dwarfism In mice hereditary dwarfism has been observed associated with the absence of the eosinophilic cells of the anterior lobe of the pituitary and it has been suggested that primary dwarfism in man represents an analogous condition

One may justifiably question if among the dwarfs classed as primary are not included many who are actually hypopituitary dwarfs Unfortunately there are insufficient data in the literature to permit definite conclusions regarding this question at the present time

Symptomatology

The primary dwarf is a true Lilliputian for except as regards his diminutive size he is mentally physically and sometimes even as regards his reproductive capacity essentially normal Even at birth the future midget may be recognized by his smallness but in many cases of this form of dwarfism the child at birth is essentially of normal weight The height of a troupe of 11 circus midgets reported by Ecke[13] varied from 101 to 129 centimeters In only two of this group were the reproductive organs apparently normal the others manifesting infantilism as well as dwarfism

The body proportions of the primary dwarf are normal However the face has a childish appearance due to the small nose and receding chin The skin sometimes is wrinkled as in geroderma

The osseous development in primary dwarfism is normal except for retardation of osseous development and abnormalities of the epiphyses of many bones particularly those subjected to greatest weight viz the hips and navicular bones of the feet There is no dysgenesis of the epi

physeal cartilages such as is observed in the hypothyroid dwarf[3] The epiphyses remain open at advanced age and the centers of ossification often are infantile and at times supernumerary In the 11 dwarfs of Ecke's series[13] whose average age was 29 years the bone age as determined roentgenologically was only 13 years[13] The nasal sinuses are juvenile in their appearance in the x ray The head of the femur may be affected and resemble that observed in Perthe's disease[13]

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DWARFISM DUE TO PRIMARY OSTEOCHONDRAL MALFORMATIONS

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CHONDRODYSTROPHIA FETALIS ACHONDROPLASTIC DWARFISM

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dystrophica The fact that it is due to failure of bony growth at the diaphysis has also suggested the designation *diaphyseal aclasis*

Chondrodystrophy is a congenital disorder originating during fetal life many probably the majority of these dwarfs die in utero the deformed fetus being aborted early or still born It is only in instances when the disorder first affects growth at a late period of fetal life with a resulting lesser degree of deformity that survival to maturity may occur [9]

Etiology

Numerous theories have been advanced to explain the etiology of chondrodystrophy The disorder has been attributed to increased hydrostatic pressure with infolding of the amnion during early embryonic life[4] The fact that chondodystrophy may appear in only one of twins speaks against this hypothesis

The bull dog calf which occurs among the Dexter breed of cattle[10] resembles in many respects the phenomenon of chondrodystrophy in man However this anomaly in cattle is accompanied by a febrile reaction in the mother during gestation whereas in the human there is no evidence of any infectious disorder occurring during pregnancies resulting in the birth of chondrodystrophic offspring In the chick embryo also micromelia may be induced by a prenatal nutritional deficiency[33] but this condition resembles osteogenesis imperfecta histologically rather than chondrodystrophy nor is there any evidence that a similar factor plays any part in man

Several of the endocrine organs have been held responsible for the development of the disease which has been attributed to hypothyroidism hypopituitarism malfunction of the thymus and hypergonadism There is nothing to substantiate these views for chondrodystrophy is not accompanied by any evidence of any known endocrine disturbance nor do the endocrine glands manifest any demonstrable pathological changes in the disorder

In view of the demonstrated hereditary factor in chondrodystrophy[39] it is logical to attribute the disorder to some congenital defect inherent in the germ plasm rather than to any of the more specific conditions described above Cases are on record in which achondroplastic dwarfs have occurred in three successive generations[18,49] The children of such dwarfs may however be normal the disorder appearing as a recessive character adhering to the Mendelian law of inheritance It is not sex linked being transmissible by either parent

Pathology

Chondrodystrophy is a result of a disturbance in development of the epiphyseal cartilages Normally the linear growth of bones occurs at the diaphysis where the shaft is contiguous with the epiphyseal cartilage As long as the layer of cartilage intervenes between the diaphysis and epiphysis growth may continue but following calcification closure of the epiphysis all growth in a longitudinal direction ceases In chondrodystrophy fetalis mucoid degeneration of the epiphyseal cartilage occurs in utero thereby arresting bone formation at the diaphysis and resulting in the micromelia characteristic of the disorder Formation of bone from periosteum is however not affected since the disorder primarily involves the cartilages and not the process of ossification Hence the bones may grow in thickness resulting in a shortened but normally thickened and strong shaft The growth of the flat membranous bones also remain undisturbed permitting their subsequent growth to normal dimensions

The disturbance of the epiphyseal cartilages just described may occur at a very early period in fetal life in which case the fetus at birth which usually is stillborn has extremities which are so shortened as to resemble fins It is only when the disturbance takes place later in pregnancy that survival to maturity may occur The atrophy of the growth cartilage with closure of the epiphyses may be evident in the x ray during fetal life permitting diagnosis of the disease before birth

There is considerable variation in the number of cartilages affected the degree to which they are altered and the histological picture[9] Kaufmann divided the chondrodystrophies into (1) hypoplastic in which the *proliferating cartilages produce an insufficient number of longitudinal* rows (2) hyperplastic hap hazard growth of cartilage in thickened masses and (3) malacic soft cartilage The observed forms rarely conform strictly to these divisions but usually represent combinations of the several varieties The commonest of the observed types is the hypoplastic the hyperplastic is the rarest

The disproportion of skeletal development in chondrodystrophy is due to the fact that certain parts of the skeleton undergo marked changes while others remain relatively unaffected The bones of flat or membranous origin for example the frontal and parietal bones of the skull the clavicles and ribs usually grow normally The extremities on the other hand particularly their proximal segments are short Due to relative shortening of the ulna and tibia as compared to the radius and fibula respectively bowing occurs In conformity with the well developed muscles is the enlargement of the ridges at the points of their

attachment The growth of bone from the periosteum results in a prominence of the joints which often are invaded thereby limiting their motion

The vertebral column may escape involvement but usually the vertebrae are wedge shaped resulting in marked lordosis Occasionally kyphosis is observed The head appears to be enlarged in comparison with the height of the achondroplastic dwarf but in actuality it is but slightly abnormal in size The skull is brachycephalic with depression *of the root of the nose due to maldevelopment of the tribasilar bone* the single bone resulting from the fusion in infancy of the occipital and temporal bone at the base of the skull is designated as the tribasilare Normally the basilar process develops from three centers but only one usually is present in chondrodystrophy resulting in a shortened basilar process a steep clivus with a small pituitary fossa and the depression of the bridge of the nose as already noted

The hands in chondrodystrophy are characteristic being short thick and shaped like a trident This peculiarity results from the equality in length of the fingers and their divergence like the prongs of a trident due to enlargement of the wrist bones The pelvis[40] also is deformed and contracted in a characteristic manner There is usually a general contraction of the pelvis but in some cases stenosis of the sacral canal with marked retardation of growth of the innominate bone is the predominant abnormality There is frequently asymmetry of the acetabula the neck of the femur being absent with changes resembling those of coxa vara[9]

Symptomatology

The extent of the deformities and the degree of dwarfism vary considerably in chondrodystrophy both as regards the number of epiphyses affected and the degree of their involvement[29] The claim has been made that abortive forms of the disorder in which only a slight degree of shortening of the extremities occurs may be encountered but this is improbable The use of the terms chondrohypoplasia chondrodystrophic habitus and chondrohypoplastic constitution thus are not justified

The height of 117 achondroplastic adults analyzed by Gunther[46] varied from 89 to 144 cm with an average of 118 cm Only 11 of the entire group exceeded 130 cm in height The diagnosis of achondrodystrophy thus becomes improbable in individuals taller than 141 cm An interesting characteristic of the achondroplastic dwarf is the absence of the sexual dimorphism so characteristic of normal animals male and female achondroplastic dwarfs attain on the average an equal stature[48]

The chondrodystrophic dwarf even on superficial inspection presents a typical appearance which is distinctive and permits easy differentiation from other forms of dwarfism[19] The apparently large sized head with its broad face depressed flat nose thick eye lids and lips giving at times a bull dog appearance the normal sized torso the abnormally shortened arms and legs the well developed musculature trident shaped hands protruding abdomen enlarged buttocks lumbar lordosis and normally developed external genitalia make the recognition of chondrodystrophy easy The extremities frequently are deformed genu varum being characteristic although genu valgum occurs in some instances Dentition is normal [3]

The achondroplastic dwarf is physically strong and mentally normal except for traits due to social maladjustment because of the deformity The reproductive organs are normally developed the hypersexuality frequently manifested being probably a compensation for an inferiority complex engendered by the dwarfed stature rather than a result of organic hypergonadism In the female menstruation and ovulation are normal and many cases of pregnancy are on record [48] delivery requiring Caesarean section due to the pelvic dystocia described in the preceding section

Diagnosis

The diagnosis of chondrodystrophia fetalis usually presents no difficulties being evident on casual inspection from the nature of the deformities as outlined in the preceding section Examination by the x ray reveals the closure of the epiphyses which can be detected even in fetal life[5] The disorder if not severe may not be recognized at birth being first brought to the attention of the parents by the fact that walking is delayed and painful

In the differential diagnosis it is necessary to exclude the other rare osteochondral disturbances described subsequently as well as certain other forms of micromelia as encountered for example in familial pleonosteosis The chondrodystrophic dwarf is readily differentiated from the cretin by his normal mental and muscular development In rare instances confusion with rickets may occur but the two conditions are readily differentiated by the x ray[49]

Treatment

As in the case of primary dwarfism there is no available method of treatment for chondrodystrophia fetalis Because of its hereditary nature

attachment The growth of bone from the periosteum results in a prominence of the joints which often are invaded thereby limiting their motion

The vertebral column may escape involvement but usually the vertebrae are wedge shaped resulting in marked lordosis Occasionally kyphosis is observed The head appears to be enlarged in comparison with the height of the achondroplastic dwarf but in actuality it is but slightly abnormal in size The skull is brachycephalic with depression of the root of the nose due to maldevelopment of the tribasilar bone the single bone resulting from the fusion in infancy of the occipital and temporal bone at the base of the skull is designated as the tribasilare Normally the basilar process develops from three centers but only one usually is present in chondrodystrophy resulting in a shortened basilar process a steep clivus with a small pituitary fossa and the depression of the bridge of the nose as already noted

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may be retarded also but dwarfism is not pronounced and is over shadowed by the specific malformations characterizing these disorders (For further discussion of oxycephaly see Vol V Chapt XLIII-A of Oxford Medicine under the heading Acrocephaly and of *leontiasis ossea* see Vol V Chapt XLIII-B)

Renal Dwarfism

Definition — By renal dwarfism one refers to a clinical syndrome rather than to a specific disease in which short stature is associated with evidence of renal dysfunction and changes in the bones resembling that seen in juvenile rickets The condition also is referred to frequently as *renal rickets* However since the deformities and osteoporosis of the skeleton are not due to avitaminosis D it is incorrect to refer to the condition as renal rickets It would be better to drop the term renal rickets from usage and adhere to renal dwarfism which implies only the coexistence of renal disease with retardation of growth Some confine the use of the term renal rickets to patients with chronic interstitial nephritis and skeletal changes but this limitation merely adds to the confusion[37]

Several varieties of this syndrome have been described and designated by special terms For example instances in which low phosphorus rickets renal glycosuria acidosis and dwarfism are prominent are sometimes referred to as *de Toni Fanconi disease*[21] Rickets with hypophosphatemia dwarfism chloride acidosis and calcification of the pyramids have been designated as *nephrocalcinosis with rickets and dwarfism* However since nephrocalcinosis may occur in several forms of renal dwarfism chronic interstitial nephritis tubular dysfunction hyperparathyroidism the use of this term is of little value Because of the infantilism which so often accompanies the condition the term *renal nanism* has been used[39] The changes in the bones in some cases resemble those of osteitis fibrosa rather than rickets and hence the designation *juvenile osteitis fibrosa* has been suggested[1] to indicate the rôle played by the parathyroid glands in the pathogenesis of the disorder

It is obvious from the preceding discussion that the manifestations of the disease under consideration are variable and manifold Confusion has resulted from the use of many descriptive terms each implying some assumed etiological factor or some pathological finding considered to be of preeminent importance We shall in the present chapter use the designation renal dwarfism to include all cases in which skeletal deformities and renal dysfunction are associated It must be remembered that any prolonged renal disease leading ultimately to renal dysfunction

reproduction by those suffering from this disorder should be discouraged Where marked deformity of the extremities occurs prosthetic operations are indicated if movements are too greatly limited

Some excellent illustrations as well as a further discussion of chondrodystrophy may be found in Vol IV Chapt XVI of Oxford Medicine under the heading Achondroplasia

Other Primary Osteo-Chondral Malformations

Several other rare primary malformations of the bones and growth cartilages occur which in some instances result in retardation of growth Dwarfism is not however a striking part of the clinical picture as observed in these disorders

Hereditary chondrodysplasia is characterized by the presence of multiple cartilaginous and bony exostoses at the diaphyseal ends of the bones with irregularity and delay in ossification of the epiphyseal cartilages The latter persist as voluminous masses and cause deformity of the affected joints Osteo cartilaginous masses may be found also in the metaphysis The condition may be unilateral or bilateral It may manifest itself in many forms and has been designated by a variety of names Ollier s disease Morquio s disease (see Oxford Medicine Vol V Chapt XLIII) rachitiform endochondrosis etc all of which represent probably only different forms of a single disorder The dwarfism in these cases usually is only slight although bowing with deformity of the limbs is common The condition is readily diagnosed by roentgenological examination[31]

In *multiple congenital enchondrosis dyschondroplasia* there is a proliferation of bone and cartilage in the end of the metaphysis forming an expansion at the joint with disturbance of growth in the affected bones Some consider this condition to be only another form of chondrodysplasia and not a unique disorder This view would seem probable on the basis of the known facts Rare osteo chondral abnormalities have been described which fail to conform to either of the above described disorders[4]

Hereditary osteogenesis imperfecta osteopsathyrosis is a congenital disease characterized clinically by blue sclerae brittle bones deafness and hypermobility and relaxation of the joints Those subject to this disorder usually are small in stature but this is not always the case The condition is assumed to be due to an hereditary congenital defect of the germ plasm resulting in hypoplasia of the mesenchyme[8] (For illustrations of this see Vol IV Chapt XVI of Oxford Medicine

In *oxycephaly steeple head leontiasis ossea* and *microcephaly* growth

Although in most cases the presenting symptoms are due to uremia in some instances the osseous deformities are outspoken and the clinical picture is that of renal dwarfism[4] The usual signs of chronic renal insufficiency observed in polycystic kidney and the demonstration of enlarged kidneys by palpation or by pyelogram make the diagnosis evident

Lesions of the urinary tract including valves of the urethra ureteral and urethral strictures and congenital contracture of the neck of the bladder may lead to hydronephrosis and renal insufficiency which in turn may give rise to renal dwarfism The clinical picture in these cases is similar in many respects to that observed in polycystic kidneys or in chronic nephritis to be described next

Chronic nephritis is responsible for the majority of cases of renal dwarfism observed clinically This renal disturbance usually is designated particularly in the older literature as chronic interstitial nephritis or in cases in which calcification of the renal pelves is evident as nephrocalcinosis In view of the questionable renal disturbance the designation chronic nephritis would seem most appropriate Many limit the designation renal rickets to the dwarfism due to chronic nephritis together with that due to congenital defects of the kidney or urinary tract but as already indicated the use of the term rickets in this connection is undesirable Among 200 case of chronic nephritis collected from the literature by Mitchell[17,35] renal dwarfism was present in 78

The presence of a pathological renal disturbance conforming to the designation chronic interstitial nephritis is evidenced by the clinical and laboratory as well as by the pathological findings in the kidneys at autopsy How the condition originates is not however always clear since frequently there is no history of an acute nephritis Some have therefore assumed that some other primary disturbance of the pituitary diencephalon etc is the basis for the disease This view is however unlikely[9,11]

The third type of renal dwarfism in our present classification is one which has been defined least clearly in the past Chronic tubular dysfunction is assumed to occur as a result of a congenital functional disorder of the renal tubules This disorder affects certain functions normally performed by the renal tubule and results in the chloride retention ketonemia acid base imbalance etc characteristic of the condition It is readily conceivable how a congenital defect of the tubular cells can result in acidosis hyperchloremia etc which secondarily cause a perversion of the normal calcium metabolism and changes in the bones

Many cases of renal dwarfism described in the literature[9] conform to the grouping just described The principal findings are acidosis which is marked a normal or reduced calcium content of the blood chloride

will induce changes secondarily in the bones[25] It is to be expected therefore that any condition leading to chronic renal disturbance during the period of growth may lead to dwarfism and that the resulting syndrome will vary in its manifestations depending upon the etiology in any given case

Classification

Much of the confusion encountered in dealing with renal dwarfism has resulted from the fact that we are dealing apparently with a clinical syndrome the external manifestations of which dwarfism due to skeletal changes and disturbed renal function are very similar but the etiology clinical course symptomatology and laboratory findings may show great variability This state of affairs results from the fact that renal disturbances due to a variety of causes congenital lesions and dysfunction infection metabolic disorders hyperparathyroidism all induce changes in mineral metabolism which in turn cause disturbances in the skeleton and retard growth

The cases of renal dwarfism described in the literature may be classified as follows

I Renal dwarfism due primarily to disturbance of the kidneys or urinary tract
   1 Congenital defects and lesions of the kidney or urinary tract
   2 Chronic nephritis
   3 Chronic tubular dysfunction including nephrosis

II Renal dwarfism associated with renal disturbances induced by extrarenal factors
   1 Endocrine disease
      Hyperparathyroidism juvenile osteitis fibrosa cystica
   2 Metabolic disturbances
      Cystine storage disease

According to the above classification there are at least five distinct conditions which may lead to the clinical syndrome designated as renal dwarfism Although differentiation of these varieties of the disease is not always easy the clinical and laboratory findings in most cases permit one to determine to which of the five conditions the disease is due

Etiology

Congenital defects of the kidney most commonly polycystic kidneys are accompanied by retardation in growth and general development

than general symptoms common to the entire heterogeneous group of disorders

The changes in the bones and retardation in growth are striking The bones are poorly calcified and show generalized osteoporosis Because of the stress of weight bearing deformity of the legs genu valgum occurs The gait usually is waddling and when the disease has progressed the patient may require the use of a crutch and ultimately even this form of locomotion becomes impossible Fractures may follow slight injury and are at times the first symptom to attract attention On inspection the large head conical pigeon shaped chest costochondral enlargements poorly developed musculature and bowed extremities immediately suggest the rachitic appearance responsible for the designation renal rickets[10] For an illustration of a renal dwarf see Oxford Medicine Vol III Chapt XI-A

The renal disturbance gives rise to polyuria polydipsia and nocturia which usually are early symptoms Ultimately the symptoms of uremia which may recur particularly with infections supervene

Patients with renal dwarfism usually are ill nourished Their skin is dry and coarse and often shows a patchy yellowish brown discoloration Secondary anemia is common Although delayed sex development and infantilism are common in renal dwarfism puberty with normal sexual maturity is observed in some patients

Diagnosis

The diagnosis of renal dwarfism usually entails no difficulty being evident from the skeletal deformities and renal disturbances Roentgenological examination reveals in an advanced case generalized decalcification of the skeleton the epiphyseal changes characteristic of rickets evidence of old fractures which are frequent absence of the lamina dura about the teeth and dense deposits of calcium in the pyramids of both kidneys and at times in other soft tissues It is usually difficult however to determine the etiology of the renal dwarfism from the roentgenogram laboratory examinations being necessary to arrive at the more exact diagnosis

The appearance of the bones in the x ray resembles that seen in the experimentally induced low calcium high phosphorus diet In the hands of an experienced roentgenologist the x ray picture may allow differentiation of renal dwarfism when advanced from that of true rickets In renal dwarfism there is a greater translucency of the shafts of the long bones and flat bones which show a more porous appearance than is

retention and hypophosphatemia At autopsy large kidneys are found which show degenerated vacuolated fatty tubules in contrast to the atrophic granular kidneys observed in chronic nephritis Albuminuria may be pronounced In some cases renal glycosuria a reduced blood sugar tolerance and ketonemia de Toni Fanconi disease are present These abnormalities have been attributed to hepatic or pancreatic disturbance but can be explained better as due to tubular dysfunction with a disturbance of the normal renal thresholds for glucose and ketone bodies

Some have designated the form of renal disturbance just described as nephrotic but since albuminuria is slight refractile bodies are absent from the urinary sediment the urinary sodium chloride quotient is normal and edema is absent the condition obviously can not be classed as a nephrosis Renal dwarfism in true nephrosis is exceedingly rare only a few cases reported in the literature conforming to this group They have therefore been included among the chronic tubular dysfunctions rather than as a separate grouping

Hyperparathyroidism in childhood as in the adult ultimately leads to renal insufficiency and deformity of the skeleton Objection may logically be raised against denoting this condition correctly called *juvenile osteitis fibrosa cystica* as renal dwarfism rather than as a specific entity of endocrine origin However the clinical picture conforms to the designation renal dwarfism[6] and the few cases on record have been diagnosed as renal rickets They may for convenience therefore be considered here

The fact that the parathyroid glands are enlarged in most cases of dwarfism has suggested that these glands are responsible for the skeletal manifestations of the disorder even in chronic nephritis This view is improbable It is only where true adenomata of the parathyroids occur in contrast to the generalized hyperplasia observed in nephritis with hypercalcemia and osteitis fibrosa cystica that the designation renal dwarfism due to hyperparathyroidism is justified

The clinical aspects of *cystine storage disease* are those of renal dwarfism[7, 8] Cystine when fed to experimental animals has been demonstrated to induce renal lesions It is logical therefore to ascribe the renal rickets and dwarfism observed in cystinuria to the toxic effect of the accumulated cystine which due to some metabolic disorder is not utilized as it is normally

Symptomatology

The symptoms in renal dwarfism vary to some extent according to the etiology of the disturbance in any given case There are however cer

TABLE I

	Chronic Nephritis	Tubular Dysfunction	Hyperparathyroidism
Blood calcium	Tendency to *hypocalcemia*	Normal or slightly *reduced*	Markedly elevated except *in case of hyperphosphatemia*
Inorganic phosphate of blood	Elevated	Reduced	Reduced
Non protein nitrogen	Elevated	Normal or moderately elevated	Normal
CO_2-combining power	May be reduced	Reduced	Normal
Glycosuria	Absent	May be marked	Absent
Ketones of blood	Normal	Elevated	Normal
Serum chloride	Low	Elevated	Normal
Anemia	Present	Absent or slight	Absent

In the rare instances of renal dwarfism due to cystine storage disease diagnosis may be made by the demonstration of cystinuria or by the observation of crystalline deposits of cystine in the conjunctiva and cornea[7] Slit lamp examination of the cornea is indicated

Treatment

The treatment in most cases of renal dwarfism is only palliative the kidney damage being progressive and leading ultimately to death in uremia If the disturbance in renal function be due to a congenital obstruction along the urinary tract urological intervention is indicated and if performed before too much renal damage has been done may give good results[3] In cases of juvenile osteitis fibrosa cystica removal of the parathyroid adenoma is indicated and would be anticipated to give recoveries as striking as those seen in the adult suffering from the same disorder

In cases of renal dwarfism due to what we have described as a primary functional tubular disorder and in which acidosis is the fundamental disorder measures designed to counteract the acidosis hyperchloremia and negative calcium balance are indicated A remarkable degree of recovery in one such case with restoration of growth has been reported by Albright and his collaborators[1] These authors administered a high calcium high phosphorus diet 2 glasses of milk three times a day vitamin D a salt poor diet and 20 c c of a mixture containing 140 gm of citric acid and 98 gm of sodium citrate in 1 000 c c of water three times daily Marked restoration of growth with alkaline therapy has

observed in ordinary rickets[14] This is not always the case in very young children In the case of renal dwarfism due to hyperparathyroidism the presence of giant cell cysts and the distinctive bone changes seen in osteitis fibrosa aid in differentiating this form of the disorder The epiphyseal changes characteristic of renal dwarfism due to primary renal disease are absent also in hyperparathyroidism unless the latter is complicated by renal insufficiency of severe degree

The usual laboratory findings of the blood and urine permit one to evaluate the degree of renal insufficiency and aid in establishing the exact diagnosis Blood studies of the calcium phosphorus phosphatase protein non protein nitrogen serum chloride and the carbon dioxide combining power should be made in addition to the usual tests used for evaluating the renal function In cases of renal dwarfism due to hyperparathyroidism the calcium level is high as it is in adult hyperparathyroidism A normal level of serum calcium speaks against hyperparathyroidism unless the serum proteins are abnormally low or there is marked phosphate retention due to secondary renal insufficiency in which cases the serum calcium may be normal or only slightly elevated

In renal dwarfism due to chronic interstitial nephritis and to congenital anomalies of the kidneys or urinary tract the usual findings of chronic nephritis are observed viz phosphate retention with a tendency to hypocalcemia nitrogen retention reduction in the phenolsulphonphthalein excretion a fixed specific gravity a low blood bicarbonate level with a tendency to acidosis etc In renal dwarfism due to congenital tubular dysfunction on the other hand the inorganic phosphate of the blood is reduced below normal acidosis is marked and the evidence of impaired renal excretory function is less pronounced The non protein nitrogen in this condition may be normal or only moderately elevated Acidosis on the other hand is marked with a low carbon dioxide combining power and hyperchloremia Albuminuria usually is present but is not marked Secondary anemia commonly present in chronic nephritis also is not striking in renal dwarfism due to tubular dysfunction Glycosuria an abnormal sugar tolerance and ketonemia are encountered sometimes in this condition

Table I summarizes some of the more important findings useful in the differential diagnosis of several forms of renal dwarfism

In renal dwarfism due to nephrosis the usual findings characteristic of this form of renal disturbance are encountered edema marked albuminuria an inverted albumin globulin ratio hypercholesterolemia a normal blood non protein nitrogen and the presence of refractile bodies in the urinary sediment

considered as responsible for abnormalities of growth but the evidence upon which this view is based is inconclusive[2]

The gonads have long been recognized as influencing growth as evidenced by the increased height attained in the pre pubertal castrate Normally maturity of the gonads stimulates closure of the epiphyses this process being delayed if puberty is prevented by castration The gonads thus act to limit growth[22] Contrariwise precocious maturity macrosomia praecox of the gonads induces premature closure of the epiphyses and cessation of growth Hence in the rare cases where precocious puberty occurs at an early age the patient on reaching adulthood will be dwarfed This form of dwarfism is however encountered very rarely[19] In this connection it may be noted that growth in height may be accelerated indirectly when sexual development is hastened through gonadal stimulation by the use of gonadotropic substances[1] These have little effect on the bone age and do not hasten epiphyseal closure in spite of their effect on linear growth[8]

Pituitary Dwarfism

Insufficiency of the anterior lobe of the hypophysis during childhood results in retardation of growth Usually this is not sufficient to cause true dwarfism the victims of the disorder being merely reduced in size and infantile in development Pituitary dwarfism as the condition is designated occurs only rarely There has been a tendency to attribute many cases of retarded growth to hypophyseal deficiency without justifiable grounds on the erroneous assumption that the hypophysis is the sole regulator of growth

Etiology

Since integrity of the hypophysis is essential for normal development *any hypophyseal deficiency during childhood* will result in retardation of growth Pituitary dwarfism is due to insufficiency of the anterior lobe of the hypophysis which may be induced by (1) intrinsic changes occurring in the anterior lobe itself and (2) by insufficiency induced by pressure from tumors hypophyseal duct cysts craniopharyngiomata or other intra or para sellar growths which interfere with the function of the hypophysis

Primary insufficiency of the anterior lobe may result from embolism thrombosis or inflammatory reactions due to encephalitis syphilis tuberculosis or other infections This leads to fibrous atrophy similar to

been reported also in cases of so called renal rickets[4] In counteracting the acidosis attention should be directed to the possibility of precipitating tetany due to the coexisting hypocalcemia Because of the electrolyte imbalance observed in tubular dysfunction the use of foods rich in potassium bananas potatoes with abstinence from meat and sodium chloride has been advocated[11] [1], but this is less rational than the alkalinizing, high calcium high phosphorus diet described above

Except in the instances noted above where therapeutic intervention is possible the prognosis in most cases of renal dwarfism is poor Among the approximately 100 cases recorded in the literature death in uremia *almost invariably resulted during the second decade of life*[18] For a further brief discussion of so called renal rickets see Oxford Medicine Vol IV Chapt X under the heading Renal and Coeliac Rickets

Dwarfism of Endocrine Origin

The recent advances in endocrinology have furthered our knowledge of several forms of dwarfism due to disturbance of the organs of internal secretion[25] Because of the very obvious effects which abnormalities of certain endocrine organs exert on the growth processes there has been a tendency to attach the stigma of endocrine disturbance rather indiscriminately to many forms of dwarfism *e g* to simple dwarfism and chondrodystrophy which as we have already seen are not associated with any disturbance of endocrine function

The endocrine organs including the hypophysis probably exert their effects on growth through their action on general metabolic processes In the absence of normal hypophyseal or thyroid function for example many metabolic functions of the tissues are interfered with as a result of which growth processes become slowed[5] With moderate or slight degrees of endocrine deficiency growth is retarded only partially

In addition to the dwarfism due to pituitary and thyroid disturbances which will be discussed in detail later other endocrine organs are involved in the growth process very rarely and need only be mentioned briefly here Any fundamental illness in which cachexia is a prominent symptom interferes with growth Hence diabetes mellitus if severe and uncontrolled will result in interference with normal growth In adrenal cortical insufficiency growth is abated[3] The fact that this condition occurs so rarely in children and is rapidly fatal explains why dwarfism secondary to adrenal cortical insufficiency is observed so rarely

Parathyroid hyperfunction as a cause of certain cases of renal dwarfism has been discussed already The thymus and pineal have both been

the aged appearance of the patient (The term should not be confused with progeria a specific disorder described later) These individuals appear to be precociously senile The skin is thick loose and wrinkled and lacks the normal subcutaneous layer of fat The fingers are short and fat due to overgrowth of the soft tissues This type of dwarf often lacks the graceful proportions observed in Lorain infantilism[43 44 47]

In addition to the symptoms due to retarded growth and development the pituitary dwarfs may manifest also signs due to increased intracranial pressure if the condition be due to tumors or cysts or to hypophyseal deficiency decreased basal metabolic rate decreased sugar tolerance tendency to infections etc

Diagnosis

The diagnosis of pituitary dwarfism can be made with certainty only when there exists either some other definite evidence of hypophyseal dysfunction or signs of an intracranial growth In craniopharyngiomata calcification may be detected by the x ray in about 80 to 90 per cent of the cases This in conjunction with other evidence of the presence of an intracranial growth permits a diagnosis with certainty The presence merely of a small sella or of bridging of the clinoid processes is no evidence of hypophyseal deficiency

Pituitary dwarfism is distinguished from hypothyroidism by the normal mental development in the former The absence of osteochondral deformities readily distinguishes it from the hypothyroid group of dwarfs The presence of normal sexual development indicates a diagnosis of primary dwarfism but where infantilism is present frequently it is impossible to decide to which group the patient belongs Many classify all such dwarfs as pituitary which if confirmed by further study would place the classification on a sounder basis

Treatment

There have appeared numerous reports in the literature of successful treatment of pituitary dwarfism with stimulation of growth by the injection of anterior pituitary extracts[43 47] In view of the available experimental data results must be viewed with some scepticism On theoretical grounds one would certainly anticipate good results to follow substitution therapy with anterior pituitary extracts but such preparations of demonstrated potency are not available as yet In evaluating the effects of therapy it must be remembered that spurts of growth oftimes occur in the

that observed in Simmonds disease of adulthood More commonly pituitary dwarfism is associated with cystic atrophy of the gland The origin of this disturbance is not always evident at autopsy In most cases the process appears to be in the nature of a chronic granulomatous lesion due to infection involving the gland or secondary to a primary cystic degeneration[18]

Pituitary dwarfism secondary to extrasellar growths is of more common occurrence and better understood many cases having been studied with correlation of the autopsy and clinical findings The cranio pharyngioma and other supra sellar growths responsible for this condition give rise to the *Frohlich syndrome dystrophia adiposogenitalis* in which adiposity with failure of development of the reproductive organs occurs without interference with growth These symptoms probably are hypothalamic in origin[2] It is only when the cysts are sufficiently large to cause pressure atrophy of the anterior lobe or when intrasellar cysts or tumors occur which press directly on the gland that *pituitary dwarfism* results[17]

Lesions of the mid brain may be accompanied also by dwarfism similar to that observed in pituitary disease[3] In these cases the anterior lobe is intact at autopsy Thus in the patient reported by Apitz[2] there was no apparent deficiency of the anterior lobe of the pituitary but an interruption of the normal hypothalamic pituitary connections Many of the cases of primary dwarfism undoubtedly belong to this group Unless one assumes that lesions of the hypothalamus may induce insufficiency of the anterior lobe without evidence of any atrophic changes in the gland it is necessary to postulate that mid brain lesions alone are capable of retarding growth The latter hypothesis would seem most probable

Symptomatology

The pituitary dwarfs are of several clinical types Many conform very closely to the *Lorain type of infantilism* the subjects of which are delicately built but normally proportioned[16] They remain sexually infantile The skeletal framework is small and fragile The epiphyses remain open and capable of osteoplastic proliferation thereby permitting growth even during the third decade of life The cranial sutures and fontanelles fail to close in infancy Dentition is delayed the milk teeth frequently persisting The distal extremities are short and the fingers small and graceful

The second type of pituitary dwarf differs from the Lorain variety just described by its progeric manifestations By progeric one refers to

flat as in infancy The skin hair and other epidermal structures also undergo the characteristic changes associated with hypothyroidism However in many cases particularly if the deficiency is of mild degree the skin and subcutaneous tissues may not be abnormally thickened nor are the hair and other epidermal structures obviously affected It is in these cases that the existence of hypothyroidism commonly is overlooked

The hypothyroid dwarf is disproportioned the upper and lower skeletal segments retaining the infantile relation and corresponding to the height rather than to the age of the patient[64] This is only true if the deficiency occurs during the period of active growth If it occurs late in childhood or is of only short duration any statural defect may be unnoticeable

The basal metabolic rate in juvenile hypothyroidism is reduced but due to the difficulties inherent in its accurate determination in children is of less value in diagnosis than it is in the adult The hypothyroid dwarf is physically sluggish and mentally backward This aids in its differentiation from other types of dwarfism As in the adult the peripheral circulation is slowed the extremities often cold the pulse pressure reduced and the cardiac output subnormal[45] The cheeks often are greyish and mottled due to the sluggish circulation[45 64]

Pathology

Hypothyroid dwarfism is accompanied by an abnormality in endochondral ossification which is designated as *epiphyseal dysgenesis*[58] Normally a single small center of ossification appears in the growth cartilage and grows out toward the margins until the epiphysis is calcified[30] In hypothyroidism the center of ossification fails to appear at the normal time Eventually ossification of the epiphysis occurs but instead of appearing at a single center multiple islets of calcification appear which ultimately coalesce The calcium deposit in the epiphyses is not orderly as in the normal but appears porous or stippled with irregular margins This abnormal type of closure of the epiphysis epiphyseal dysgenesis is characteristic of hypothyroidism The defect responsible for this phenomenon is in the cartilage rather than in the process of calcification for when closure of the epiphyses is induced by administration of dessicated thyroid the same dysgenesis is observed[3]

Diagnosis

Defective growth and development are the most characteristic structural changes observed in juvenile hypothyroidism If thyroid deficiency

pituitary dwarf and that slow growth may continue as long as the epiphyses are open

Where pituitary dwarfism is due to a tumor or cyst operative interference is to be considered In the supra sellar craniopharyngiomata evacuation of the cyst with post operative irradiation is indicated Although these cysts usually are considered to be insensitive to the x rays good results have been obtained in some instances and where operation is refused roentgen therapy should be tried

Hypothyroid Dwarfism

The commonest cause of dwarfism of endocrine origin is that due to thyroid insufficiency Where thyroid function is congenitally absent cretinism occurs Among other deficiencies of cretinism dwarfism is prominent but the other characteristic features mental deficiency lethargy pot belly etc are more conspicuous and render the diagnosis obvious On the other hand in children in whom hypothyroidism usually of a milder degree occurs after birth the classical symptoms of cretinism are absent and diagnosis is more difficult It is only in recent years that improvements in clinical chemistry and methods of roentgenology have permitted the detection of milder forms of hypothyroidism in children and focused attention on the thyroid as responsible for many instances of retardation in growth and development hitherto erroneously attributed to pituitary insufficiency or left undiagnosed[16 5]

Symptomatology

Hypothyroidism induces fundamentally the same metabolic disturbances but its clinical manifestations differ depending upon the age at which it occurs When existing prenatally or in early infancy classical cretinism follows when it develops in the adult myxedema When occurring during childhood abnormalities of growth and development are prominent in addition to the changes in the metabolism circulation and epidermal tissues observed in myxedema None of these attains the severity encountered in the cretin or in the classical case of adult myxedema

In addition to the retarded growth one observes in juvenile hypothyroidism other evidences of lack of development The eruption of the teeth is delayed usually they are defective in structure and subject to decay The naso orbital configuration fails to mature the bridge of the nose remaining

in the patient's condition with greater success than is possible in any of the other forms of dwarfism

In evaluating the effect of therapy the procedure advocated by Wilkins[54] is to be commended whereby the height bone and mental ages are recorded and followed during treatment These are obtained by comparing the patient's height the development of centers of ossification and the mental age with standard tables For example if a child aged 10 has a height corresponding to that of the normal age 8 centers of ossification developed to the stage normally observed in children aged 7 and a mental age of 6 his height bone and mental ages are respectively 8 7 and 6 It is the purpose of therapy to attempt to bring the patient to a state of normal physical and mental development The ultimate mental capacity of the hypothyroid child under adequate treatment is not strictly related to the physical growth[3] for in many cases irreversible changes or congenital mental defects are present For this reason the developmental rate especially the bone age serves as the best guide to the adequacy of therapy[54]

Inasmuch as a deficiency during childhood of the thyroid hormone may lead to irremediable retardation of growth and mental and structural development it is necessary to treat the condition intensively Doses of desiccated thyroid bordering on the toxic level should be maintained One may start in most cases with a daily dose of gr 1/2 (0 03 gm) (U S P standard) increasing the dosage at 7 to 10 day intervals by increments of gr 1/2 (0 03 gm) until toxic symptoms occur These consist of cramps diarrhea vomiting excess irritability a rapid and forceful pulse and a warm flushed skin When toxic symptoms appear the treatment is omitted for a few days and then resumed at a lower level The amount required usually varies from gr 1/2 to 3 (0 03 to 0 2 gm) daily which may be administered in a single dose

Dwarfism Secondary to General Metabolic and Cachectic Disorders

In the present section are considered a heterogeneous group of disorders in which general metabolic disturbance or prolonged cachexia induces retardation in growth which if extreme may lead to actual dwarfism Any chronic disorder which interferes with the development of the soma generally will affect also the growth process in the epiphyseal cartilages[7] Some of the forms of dwarfism already described in other chapters and sections e g that observed in uncontrolled or severe diabetes mellitus belong essentially in the present grouping

begins at an early age and remains untreated dwarfism may result but in most cases and when the deficiency occurs in later childhood dwarfed dimensions are not encountered Similar dwarfing and osseous retardation are observed also in conditions other than hypothyroidism and do not suffice for a diagnosis unless other signs of diminished thyroid secretion are present[54]

Although studies of the chemical composition of the blood are informative and often aid in arriving at a diagnosis the results are not pathognomonic As in myxedema the blood cholesterol may be elevated above the normal which in children varies from 98 to 308 mgm per cent[5] On a meat free diet the normal child excretes 0 6 to 7 8 mgm of creatine per kilogram of body weight daily In the hypothyroid individual provided with an adequate caloric intake and 2 gm of protein per kilo of body weight the creatine excretion is reduced to 0 to 3 8 mgm[55] Thus a high cholesterol level and a reduced creatinuria suggest hypothyroidism but normal findings do not exclude the existence of the disorder[46] The response to the administration of dessicated thyroid and the effect on the cholesterol level and creatine excretion of withdrawing therapy are striking and are more useful as indicators of thyroid activity as Wilkins Fleischmann and Block[55] recently have demonstrated The serum phosphatase has been used also as an aid in diagnosis being reduced to less than 4 5 units and rising to normal 7 2 units during thyroid therapy[51]

Of greatest importance in the diagnosis of hypothyroid dwarfism is the epiphyseal dysgenesis already described This abnormality is readily demonstrable in the x ray particularly in larger centers of ossification such as the head of the femur humerus and navicular bone of the foot Its presence as well as its appearance in the new centers of ossification during treatment with dessicated thyroid affords a valuable aid in the diagnosis of hypothyroidism in children Epiphyseal dysgenesis may occur also in *osteochondritis deformans Perthe s disease* The latter disorder is differentiated from the changes induced by hypothyroidism by the fact that it is a destructive lesion of the hips occurring in a previously normal epiphysis Usually it is unilateral being limited to a single epiphysis and is accompanied by pain[53]

Treatment

The recognition of hypothyroidism in childhood is worthy of the physician s keenest efforts for the availability of a cheap and effective remedy dessicated thyroid renders it possible to effect an improvement

in the patient s condition with greater success than is possible in any of the other forms of dwarfism

In evaluating the effect of therapy the procedure advocated by Wilkins[54] is to be commended whereby the height bone and mental ages are recorded and followed during treatment These are obtained by comparing the patient s height the development of centers of ossification and the mental age with standard tables For example if a child aged 10 has a height corresponding to that of the normal age 8 centers of ossification developed to the stage normally observed in children aged 7 and a mental age of 6 his height bone and mental ages are respectively 8 7 and 6 It is the purpose of therapy to attempt to bring the patient to a state of normal physical and mental development The ultimate mental capacity of the hypothyroid child under adequate treatment is not strictly related to the physical growth[3] for in many cases irreversible changes or congenital mental defects are present For this reason the developmental rate especially the bone age serves as the best guide to the adequacy of therapy[54]

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Classification

As a matter of convenience we may classify the conditions responsible for the varieties of dwarfism now to be considered as follows

I Congenital disorders
  1 Syphilis
  2 Heart disease
  3 Congenital anomalies
  4 Progeria
  5 Laurence Moon Biedl syndrome
II Nutritional Disturbances
  1 Malnutrition
  2 Parasitic infestation
  3 Scurvy
III Deforming Diseases of Bones
  1 Rickets
  2 Tuberculosis of the spine
  3 Poliomyelitis
IV Other Chronic Illnesses
  1 Abdominal tuberculosis
  2 Regional enteritis
  3 Coeliac disease
  4 Malaria
  5 Scleroderma

Congenital Disorders

Syphilis — Congenital syphilis causes retardation in growth by its general interference with body development and by its specific effects on bone growth *Syphilitic osteo chondritis* is characterized roentgenologically by a saw tooth irregularity at the edge of the ossification zone

Heart Disease — Severe cyanotic types of congenital heart disease leads to dwarfism as a result of the general interference with the nutrition of the tissues The cyanosis clubbing of the fingers and presence of a loud murmur make the etiology of the dwarfism obvious Mitral disease in childhood if severe also may interfere with growth by the same mechanism as may also other severe cardiac affections

Congenital Anomalies — Dwarfism has been associated with other rare congenital anomalies e g anomalies of the bile ducts lead poisoning of the mother during gestation duodenal stenoses etc

Progeria — This is a rare disorder only 14 cases being recorded in the world s literature It is characterized by dwarfism infantilism and premature aging The facial appearance of victims of the disorder is characteristic so that simple inspection suffices for recognition of the disease The view that progeria is due to disease of the pituitary is no longer tenable

Laurence Moon Biedl Syndrome — This syndrome is characterized by infantilism obesity atypical retinitis pigmentosa and mental deficiency Victims of the disorder may be small in stature and occasionally dwarfed[1]

Nutritional Disturbances

Malnutrition leads to retarded growth Conditions leading to mal nutrition such as coeliac disease parasitic infestation and the like may result in pronounced degrees of dwarfism and infantilism which respond promptly to specific treatment administered to relieve the primary cause of the malnutrition In scurvy there is a general nutritional disturbance in association with specific changes in the growth cartilages For other chapters in Oxford Medicine giving a further discussion of these conditions the index may be consulted

Deforming Diseases of Bones

Any disease causing deformity of the bones may lead to dwarfism In addition to the conditions already discussed in preceding sections may be mentioned rickets tuberculosis of the spine and poliomyelitis

Severe rickets particularly during infancy if left untreated may lead to dwarfism due to the malformations of the long bones and faulty calcification of the skeleton With the modern usage of vitamin D this form of dwarfism is becoming rare The presence of the rickety rosary scoliosis high forehead and bowing of the legs usually render the diagnosis obvious[14] Rare cases of so called delayed and refractory rickets may be confused with renal dwarfism For a further discussion of Rickets see Vol IV Chapt X of Oxford Medicine

Spinal caries due to Pott s disease may produce the typical hunch back dwarf Other involvements of the vertebral column may induce similar deformity with reduction in stature

Other Chronic Illnesses

Any protracted chronic illness during childhood causes a temporary retardation of growth If the condition occurs over many years the

defect in growth may lead to dwarfism Infantilism is associated with the retardation in growth and the condition therefore, has been designated as *cachectic infantilism infantilo chelnism* or *dystrophic infantilism* Individuals suffering from this form of dwarfism conform to the Lorain type of infantilism Puberty may be delayed until the age of twenty Radiological examination reveals arrested lines of growth in the diaphyses with no evidence of disproportion if the reduced size of the body be taken into consideration [7]

The common conditions associated with this form of dwarfism are abdominal tuberculosis regional enteritis coeliac disease so called coeliac *rickets and malaria Rare instances of scleroderma in childhood* believed by some to be a congenital form of this disease, have been accompanied also by dwarfism

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